A Report to the Board of Scientific Counselors
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Biomedical Imaging R&D:
Advanced Tools for Cancer Research

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Glossary

AAM Active Appearance Modeling
ACS Active Contour Segmentation
ALTS ASCUS-LSIL Triage Study
AO Anterior Osteophytes
ASCCP American Society for Colposcopy and Cervical Pathology
ASCUS Atypical Squamous Cells of Undetermined Significance
ASM Active Shape Modeling
AW Acetowhite Lesions
BMT Boundary Marking Tool
CBIR Content-Based Image Retrieval
CE Columnar Epithelium
CEB Communications Engineering Branch
CIN Cervical Intraepithelial Neoplasia
CLEF Cross Language Evaluation Forum
CCV Color Coherence Vector
DP Dynamic Programming
DSN Disc Space Narrowing
ECOC Error-Correcting Output Codes
GHT Generalized Hough Transform
GIFT GNU Image Finding Tool
GMM Gaussian Mixture Model
HREB Hormonal and Reproductive Epidemiology Branch
ImageCLEF Medical Image Retrieval extension to CLEF
IRMA Image Retrieval for Medical Applications
LSIL Low-grade Squamous Intra-epithelial Lesion
MDT Multimedia Database Tool
MedGIFT GIFT modified for medical image retrieval
NCI National Cancer Institute
NHANES National Health and Nutrition Examination Surveys
NLM National Library of Medicine
NN Neural Networks
PACS Picture Archiving and Communications Systems
PATH Program for Appropriate Technology in Health
PSM Partial Shape Matching
RF Relevance Feedback
ROI Region of Interest
SCJ Squamo-Columnar Junction
SE Squamous Epithelium
SECC Semantic Error-Correcting output Codes
SPIRS Spine Pathology and Image Retrieval System
SR Specular Reflection
STAPLE Simultaneous Truth and Performance Level Evaluation
WSM Whole Shape Matching

Biomedical Imaging Research and Development

ADVANCED TOOLS FOR CANCER RESEARCH

1   Introduction and background

Since the last review by the Board in September 2006, the biomedical imaging work of the Communications Engineering Branch has had an impact on research in the field of uterine cervix cancer prevention and is positioned to impact clinical practice in that field, as well as the assessment of professional knowledge in the field of colposcopy. CEB-developed tools, and the close collaborative work among CEB engineers and computer scientists, and medical experts in the field of gynecologic oncology have played significant roles, and are currently being used in significant ways, for the following:

- Potential development of new biopsy protocol for pre-cancer screening.
- Image-based testing for a national program of knowledge assessment in colposcopy
- Analysis of capabilities and limitations of visual evaluations of the cervix for pre-cancer detection.
- Analysis of expert interobserver agreement in visual evaluations of the cervix.
- Evaluation of non-expert health workers to screen for cryotherapy treatment for HPV-positive women.
- Evaluation of HPV Linear Array genotyping

In addition to the impact in the field of uterine cervix cancer, CEB tools and collaborative efforts have supported and are currently supporting

- Study of risk factors for Inflammatory Breast Cancer
- Phase II clinical trial of the treatment of Kaposi sarcoma by nicotine patch
- Study of the comparative efficacy of glass slide diagnosis versus virtual microscope diagnosis for lung images

Table 1 provides a summary of the collaborative work that CEB has done with NCI by study or project, including the study objectives, principal investigators, data used, and resulting publications in medical journals[1]. A world map showing the locations of sites contributing to the work is shown in **Figure 1**. The impact of selected projects are detailed in Sections 5 and 6. In this introduction we provide an overview of our past biomedical imaging work that provides context for our current efforts.

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[1] Our papers in computer science and engineering journals, and conference proceedings, appear at http://archive.nlm.nih.gov.

TABLE 1: IMPACT OF CEB TOOLS IN BIOMEDICAL RESEARCH

No.	User Group	Investigator(s)	NLM Tool(s)	Image Type	Study/Project Name	Objective	Description	Medical Journal Publications
1	**National Cancer Institute,** DCEG/HREB	NCI: Jose Jeronimo, M.D.; Mark Schiffman, M.D.	Boundary Marking Tool, Multimedia Database Tool, Virtual Microscope, Teaching Tool	Uterine cervix; digitized 35 mm color slides; Uterine cervix; digitized biopsy (histology) slides	Tool development for uterine cervix cancer research	Develop suite of software tools for archiving image and clinical text data for uterine cervix; to allow Web access to the data for research and further data collection; to provide tools for medical expert training.	100,000 digitized slides of uterine cervix; 2,000 digitized histology images. Longitudinal, multi-year data collected in Costa Rica and in the U.S. (In progress)	Jeronimo, et al. *21st International Papillomavirus Conference,* Feb 2004. Jeronimo-1, et al. *Journal of Lower Genital Tract Diseases,* Jan 2006. Jeronimo-2, et al. *Journal of Lower Genital Tract Diseases,* Jan 2006.
2	**National Cancer Institute,** DCEG/HREB	Jose Jeronimo, M.D.	Boundary Marking Tool	Uterine cervix; digitized 35 mm color slides	Lesion marking on digital images	Examine reproducibility of lesion marking; Correlation of visual diagnosis with HPV Infection	939 images, 20 expert observers (Complete)	Jeronimo, et al. *23rd International Papillomavirus Conference,* July 2006. Jeronimo, et al. *Am J Obstet Gynecol,* August 2006. Jeronimo, et al. *American Journal of Obstetrics and Gynecology,* July 2007. Jeronimo, et al. *Obstetrics and Gynecology,* 2007.
3	**National Cancer Institute,** DCEG/Viral Epidemiology	James Goedert, M.D.	Boundary Marking Tool	Skin lesions digital photos	Kaposi Sarcoma Nicotine Treatment	Evaluate regression of Kaposi sarcoma skin lesions under treatment with nicotine patch	24 patients; 950 images obtained over 15 weeks; 2 expert observers (Complete)	Goedert, JJ, et. al. *Journal of the European Academy of Dermatology and Venereology,* Sep 2008.

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4	**National Cancer Institute,** DCEG/HREB	Jose Jeronimo, M.D.; Phil Castle, Ph.D.	Boundary Marking Tool	Uterine cervix; digitized 35 mm color slides	Age-related changes of the cervix	Study correlation between amount of columnar epithelium/age to presence of carcinogenic and non-carcinogenic HPV	945 patients; 945 images; 1 expert observer (Complete)	Castle, et al. *Cancer Research,* Jan 2006.
5	**National Cancer Institute,** DCEG/HREB	Julia Gage, Ph.D.; Jose Jeronimo M.D.	Boundary Marking Tool	Uterine cervix; digitized 35 mm color slides	Multinational evaluation of a new approach for cervical cancer screening and treatment	A new approach for cervical cancer prevention based on HPV-DNA testing followed by visual inspection tested with physicians and midwives from USA, Peru, Costa Rica, Ghana, South Africa, and Thailand.	721 images, approx. 20 trained observers (midwives) in Peru (Complete)	Gage JC, et al. *An evaluation by midwives and gynecologists of treatability of cervical lesions by cryotherapy among HPV-positive women. Accepted for publication in International Journal of Gynecological Cancer.* Gage JC et al. *Treatability by Cryotherapy in a Screen-and-Treat Strategy. Accepted for publication in Journal of Lower Genital Tract Diseases.* Gage JC. *An evaluation of visual triage of human papillomavirus-positive women.* Ph.D. dissertation in epidemiology, Johns Hopkins University Bloomberg School of Public Health, 2008.

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No.	**User Group**	**Investigator(s)**	**NLM Tool(s)**	**Image Type**	**Study/Project Name**	**Objective**	**Description**	**Medical Journal Publications**
6	**American Soc. for Colposcopy and Cervical Pathology; National Cancer Institute,** DCEG/HREB	ASCCP: Dennis O'Connor, M.D.; Alan Waxman, M.D. NCI: Jose Jeronimo, M.D.	Boundary Marking Tool	Uterine cervix; digitized 35 mm color slides	Multi-expert consensus in the evaluation of digitized cervigrams to be used for training purposes	Select images with consensus among the expert colposcopists to be used for training in colposcopy.	150 images, 6 expert observers (Complete)	Massad LS. American Society for Colposcopy and Cervical Pathology and the National Institutes of Health explore research collaboration. [Editorial] *Journal of Lower Genital Tract Disease, 2006, 10(1), 1-2.*
7	**American Soc. for Colposcopy and Cervical Pathology; National Cancer Institute**	ASCCP: L. Stewart Massad, M.D. NCI: Jose Jeronimo, M.D.; Mark Schiffman, M.D.	Boundary Marking Tool	Uterine cervix; digitized 35 mm color slides	Interobserver agreement	Estimate reproducibility of expert visual evaluation of acetowhite lesions.	862 patients; 862 images, 20 observers (Complete)	Massad LS, et al. *Obstetrics & Gynecology,* Jun 2008, 111(6):1266-7.
8	**National Cancer Institute,** DCEG/HREB	Mark Schiffman, M.D.; Melinda Butch-Kovacic, Ph.D.	Virtual Microscope	Uterine cervix; digitized biopsy (histology) slides	Evaluate virtual microscope for cell counting		500 images; 1 observer (In progress)	
9	**American Soc. for Colposcopy and Cervical Pathology; National Cancer Institute,** DCEG/HREB	ASCCP: Alan Waxman, M.D.; Kathy Poole, Exec. Admin. NCI: Nico Wentzensen, M.D.; Mark Schiffman, M.D.	Teaching Tool	Uterine cervix; digitized 35 mm color slides	Medical Knowledge Assessment	Create image-based system for information collection and expert assessment over the Web	(In progress)	

	TABLE 1: IMPACT OF CEB TOOLS IN BIOMEDICAL RESEARCH							
No.	User Group	Investigator(s)	NLM Tool(s)	Image Type	Study/Project Name	Objective	Description	Medical Journal Publications
10	**National Cancer Institute,** DCEG/HREB	NCI: Nico Wentzensen, M.D.; Mark Schiffman, M.D.	Boundary Marking Tool; Multimedia Database Tool	Uterine cervix; digitized 35 mm color slides	Cervix Biopsy	Create data collection with biopsy points marked on cervix images; store actual biopsy outcomes to create set of medical outcomes correlated with spatial location data for the tissue regions.	1,000 patients; 1,000 images, from **University of Oklahoma Health Sciences Center** (In progress)	
11	**National Cancer Institute,** DCEG/Genetic Epidemiology; Center for Cancer Research / Cell and Cancer Biology	Maria Teresa Landi, M.D., Ph.D.; Ilona Linnoila, M.D.	Virtual Microscope	Lung; digitized biopsy (histology) slides	Lung Diagnosis from Digital Image	Investigate efficacy of lung cancer diagnosis from digital biopsy versus glass slides.	Approx. 200 lung histology images (In progress)	
12	**National Cancer Institute,** DCEG/Biostatistics	Catharine Schairer, Ph.D.	Inflammatory Breast Cancer Tool	Breast anatomy; digitized color photos	Case-control study of inflammatory breast cancer in North Africa and France.	Investigate causes of inflammatory breast cancer, using digitized images to confirm diagnosis by local physicians.	Images for 400 IBC cases Data is collected from two centers in Egypt, one center in Morocco, one center in Tunisia, and four private clinics in Tunisia and Algeria. (In progress)	
13	**National Cancer Institute,** DCEG/HREB	Sophia Wang, Ph.D.; Nicolas Wentzensen, M.D.	HPV Linear Array Tool	Digitized HPV Linear Array Strips	Computer Interpretation of HPV Linear Array Strips	Investigate automated reading of HPV linear array strips as aid in reducing labor required and in enhancing reproducibility of interpretations.	84 images, 1,018 patient visits (In progress)	Jeronimo, et al. *Evaluation of Linear Array Human Papillomavirus Genotyping Using Automatic Optical Imaging Software, Journal of Clinical Microbiology,* Aug 2008, 46(8):2759-65.
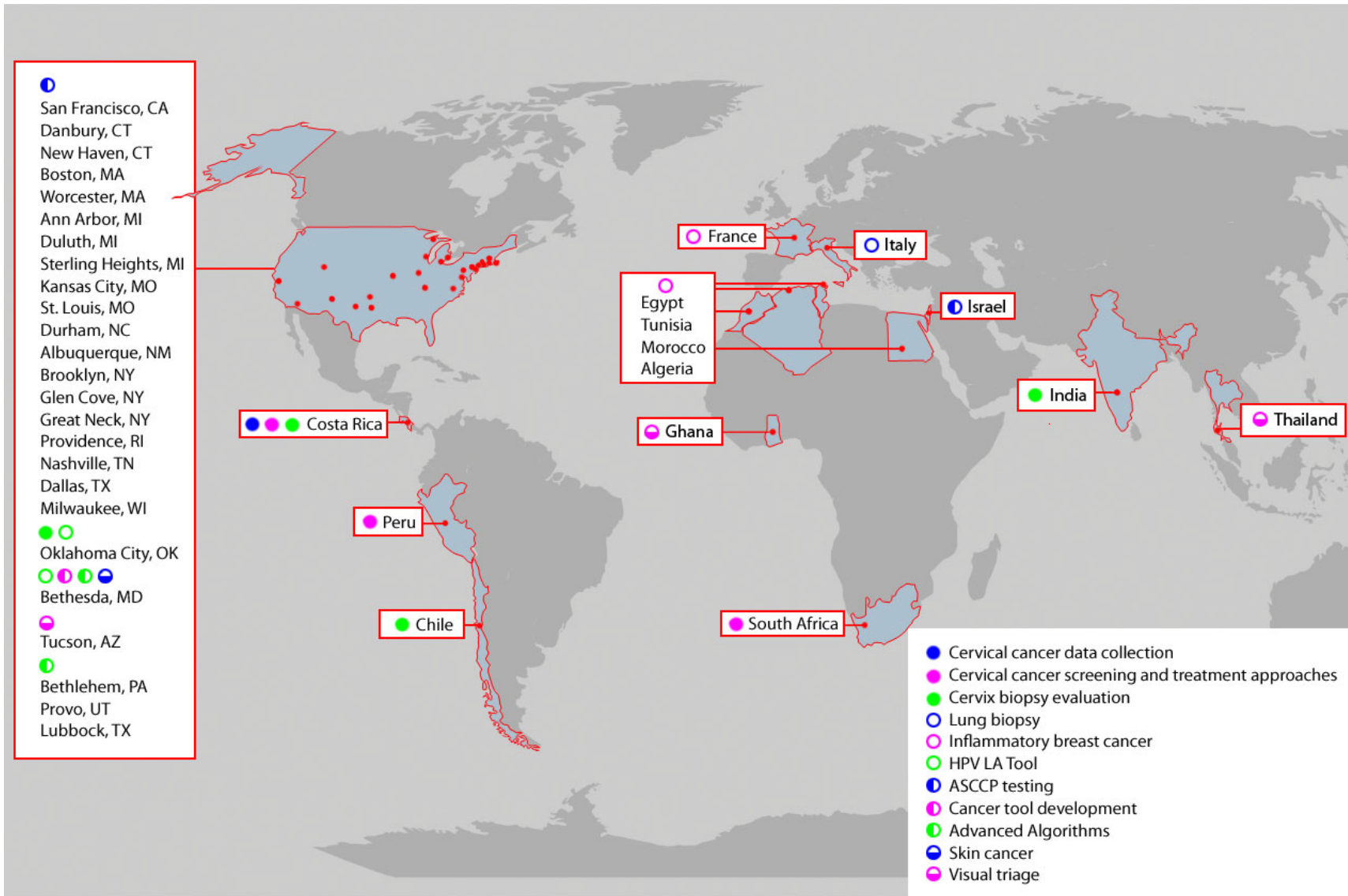
Figure 1. Sites of CEB tool use/development

Motivated by the universal acknowledgement of the critical importance of images in clinical medicine and biomedical research, the Communications Engineering Branch has had a longstanding interest in biomedical imaging research. Despite much effort, significant challenges remain in finding the best ways to archive, compress, transmit, index, access, retrieve and disseminate digital biomedical images. A particular interest is automated indexing by image content features through Content-based Image Retrieval (CBIR) techniques.

Our work in biomedical imaging originates in an effort two decades ago to preserve a collection of spine x-rays acquired as part of a periodic nationwide survey of public health conditions called the National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics (NCHS.) The second such survey, NHANES II, yielded a broad spectrum of information on each of 25,286 participants, of whom 20,322 were both interviewed and examined [**1-3**]. The data taken included medical examination data, demographic information, and blood chemistry analyses. In addition, a subset of the participants received a detailed examination that included radiographs of the cervical and lumbar spine. This resulted in a collection of approximately 17,000 films. The third survey, NHANES III [**2**], produced an additional 10,000 films of hands, wrists and knees.

The spinal x-rays and 2,000 fields of textual information from each participant in NHANES II, as well as the text data from NHANES III have been made available to the public through WebMIRS[**4**], a Web-accessible system used by a broad user community from academia, corporations, hospitals and elsewhere. Reported uses by more than 600 registrants from 59 countries include research in epidemiology and rheumatology, computer science work in algorithmic development and image processing research, and graduate education in the classroom.

While we continue to use our x-ray collection, Visible Human and other images to investigate algorithmic design for indexing, compression and solutions to other perennial problems, much of our current focus is on image collections from NCI. The images from NCI derive from two major studies. The first is the ASCUS-LSIL Triage Study (ALTS), a 2-year longitudinal study of 5,000 women with minor cervical cytologic abnormalities that yielded 40,000 cervicographic images[2]. The other similar, screening study called the Guanacaste Project [**5**] is an intensive, population-based cohort study of human papillomavirus (HPV) infection and cervical neoplasia among 10,000 women in Guanacaste, Costa Rica, where the rates of cervical cancer are perennially high. State-of-the-art visual, microscopic, and molecular screening tests are used to examine the origins of cervical precancer/cancer and to explore viral and host factors that make a geographic region 'high risk'. The Guanacaste study has completed its field phase after seven years of follow-up, and now has spawned a number of subprojects based on collected specimens, images, and outcomes, including 60,000 cervicographic images. NCI is examining several potentially important etiologic cofactors, such as chronic inflammation and endogenous hormone levels, which may contribute to cervical cancer risk. Most ambitiously, over 30,000 cervical cell and 30,000 plasma specimens are being tested for HPV DNA and antibodies, respectively, to

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[2] In this report we use the terms *cervicography*, *cervicographic image*, *uterine cervix image*, and *cervigram* interchangeably.

determine how type-specific HPV DNA types (there are over 40 types of cervical HPV) and antibodies influence outcome.

The image data collected in the aforementioned studies includes cervicography (a type of high-definition cervical photograph), Pap test, and histology images. In conventional cervical cancer prevention programs, abnormal cytology (Pap tests) triggers referral to a magnified visual assessment of the cervix following application of vinegar (5% acetic acid), a process called colposcopy. Cervicography is a low-cost alternative to colposcopy that produces similar images. Colposcopists take biopsies based on their assessment of the site of most significant disease. The resultant biopsies are used to guide treatment. While biopsy and cytology slides are saved and can be shared for research and teaching, colposcopy has not lent itself to rigorous research, since colposcopic images are not generally captured and archived. The use of stored digital images is expected to make an impact on research and education in the use of cervicographic and colposcopic images for the study and prevention of uterine cancer. It has been remarked by an expert in gynecology that colposcopy research has lagged behind other fields that have taken advantage of advances in computerization [**6**].

Our work in collaboration with NCI is to develop methods that enable exploration of visual aspects of HPV and cervical neoplasia. In etiologic studies NCI researchers can then relate the numbers of infecting viral types with numbers and positions of lesions. They will be able to follow the topographic progression and regression of lesions. For screening research NCI will use 100,000 uterine cervix images from the Guanacaste and ALTS Projects (digitized by NLM) to optimize and standardize visual screening of the cervix. Along with developing support technologies, we are developing a suite of open source applications for the purpose of (1) exploiting extensive longitudinal study data collected on subjects from the ALTS and Guanacaste projects, and (2) supporting a range of studies conducted by cancer researchers at NCI and elsewhere.

Though not discussed in this report, other imaging activities at the CEB involve document image analysis. In the Medical Article Records System (MARS) project we develop rule-based and machine learning algorithms to automatically extract bibliographic data (title, author names, affiliation, abstracts, etc.) from scanned and Web documents to populate the MEDLINE database, greatly minimizing manual effort. Another project focusing on digital preservation, System for Preservation of Electronic Resources (SPER), seeks to automatically extract descriptive metadata from scanned historic documents (using Support Vector Machine and Hidden Markov Model) to ensure access to the documents for the long term. The descriptions of these and other projects, and the publications they have spawned, are available on our Web site, http://archive.nlm.nih.gov.

We organize this report as follows. Following an outline of project significance and objectives in Sections 2 and 3, we discuss our development of eight tools for research into cervical, skin and breast cancer in Section 4 (our tool development work was awarded the 2008 IDEA Award by the Internet2 consortium.) In Section 5, we discuss the impact of these tools in research studies by several branches of the NCI and their collaborators, some of these studies completed and others ongoing. In Section 6, we elaborate on the use of one of the tools for colposcopy knowledge assessment for medical professionals. Section 7 outlines next steps, strategic

initiatives employing Content Based Image Retrieval (CBIR) techniques toward automated image segmentation and extraction of regions of interest, generation of segmentation consensus among multiple observers, an image retrieval system and its integration over the Internet with another geographically distant system (to exploit the CBIR functions of both), and efforts to find low-cost high-performance solutions to compute-intensive operations in image processing.

2   Project significance

Both NLM and NIH expert advisory groups in past years have explicitly placed high importance on incorporating image use into medical knowledge, research and practice [**7, 8**]. Table 2 below illustrates the relationship of our project work to current NLM long-range goals, as elaborated in the updated 2006 NLM Long Range Plan [**9**].

Table 2. Relationship of CEB Biomedical Imaging Research & Development to NLM/NIH Long-Range Goals

Project work	Applicable 2006 NLM Long Range Plan elements
Imaging R&D focusing on systems integration for novel solutions to high impact medical information problems	• Data mining tools and algorithms for knowledge discovery • Support integration of public health data…into clinical informatics • Develop…public health information by supporting training and research • Develop and promulgate … model programs that serve underserved populations at home and abroad • Develop open-source, translational research tools and resources, including data collection tools. • Interact closely with…the work of other individual institutes
R&D for advanced imaging solutions by use of image contents	• Data mining tools and algorithms for knowledge discovery • Develop computational algorithms and tools that can extract information from multiple biological sources…and integrate them into coherent data models • Develop open-source, translational research tools and resources, including data collection tools
R&D into evaluation of imaging solutions	• Data mining tools and algorithms for knowledge discovery • Play a leading role in encouraging…criteria for quality in clinical databases • Develop computational algorithms and tools that can extract information from multiple biological sources…and integrate them into coherent data models • Interact closely with…the work of other individual institutes

3   Project objectives

The overall goal of the project is to push the current state of image use in significant biomedical imaging domains, for example, spinal and uterine cervix images. This goal is to be achieved through the following specific objectives:

Objective 1 Develop tools to enable the collection and dissemination of new knowledge from images

This objective addresses R&D into innovative systems integration required to develop tools (applications) that support specific efforts such as the exploitation of the NCI uterine cervix data for medical analysis, training, and education. Our applications combine Java programming, Java servlets, PHP scripting, embedded SQL, the MySQL DBMS, XML, Asynchronous Java Script (AJAX), tiled image processing, and both off-the-shelf and custom-written, Wavelet-based, image compression. This work is yielding open source applications created in close collaboration with medical experts working with data of significant value to the national and international medical communities.

Objective 2 Actively support the use of our tools for the collection and evaluation of image-derived knowledge from multiple observers

Here our objective is to ensure that tool development is in synchrony with the research objectives of our biomedical collaborators. This involves introducing our tools at the earliest point at which these applications are sufficiently mature, fine tuning the tools for accuracy and performance, and enhancing them with added capabilities missing in early versions. This close collaboration also allows gathering and reconciling data from multiple experts, and deriving from this data the ground truth necessary for algorithm development.

Objective 3 Develop advanced techniques for extracting knowledge directly from image content

We are conducting R&D into developing a future generation of query and retrieval techniques that will directly use the contents of images, including such features as color, texture, and shape, which may be applied to objects within the images or to the image as a whole. This work is conducted through: **(a)** the development of algorithms for image segmentation, feature extraction, classification, similarity matching and other key stages in Content-Based Image Retrieval (CBIR); **(b)** the development of prototype systems that implement these algorithms; and **(c)** using the prototypes to evaluate and fine tune these algorithms for optimum performance for targeted image collections. CBIR is expected to play a significant role in data mining and knowledge discovery from images in the future.

Objective 4 Maintain a strong publication policy and publicly disseminate the applications developed

Our work has been, and will continue to be, published in the open literature. Further, all software will continue to be distributed as open source material, and commercial dependencies (sometimes necessary in early prototypes) eliminated to enable widespread use.

4 Imaging tools for cancer research

In this section, we outline the tools developed, most of them Web-accessible, for research or skill assessment at NCI, the American Society for Colposcopy and Cervical Pathology (ASCCP), and academic institutions.

Although the current use of these tools is predominantly by experts in the field of gynecologic oncology, *making the tools applicable to a wide domain of biomedical imaging and information needs has been a guiding development principle*. For example, the Boundary Marking Tool may be used for graphical markup and annotation of any image type that can be read by the underlying Java technology; the Multimedia Database Tool is capable of providing access to any text/image database that is compatible with its (very general) abstract data model; the Teaching Tool can administer multiple-choice image-based exams for any knowledge domain, if the images satisfy its formatting requirements for Web browser display. *In short, although the tool development has come about because of the close collaboration with the uterine cervix research community, the usefulness of the tools is by no means limited to that domain.*

The academic use of the tools is by computer science and engineering experts engaged in algorithm design for image-related information retrieval. In the following we discuss the capability of the tools, their use, and the underlying technology.

4.1 Boundary Marking Tool (BMT)

4.1.1 Capability

The identification and collection of visual features in medical images by content experts is an essential step in many research areas. The Boundary Marking Tool allows the collection of graphical mark-ups on biomedical images, as well as the collection of text annotations that are associated with those mark-ups. Using the BMT, a user may draw boundaries around regions of interest (usually tissue or anatomical regions; sometimes, more general regions, such as those containing mucus or blood) and use on-screen controls to record interpretations of these regions. This allows the acquisition of spatial data that is correlated with a specific biomedical interpretation.

Examples of BMT screens for uterine cervix data collection are shown in **Figure 2**. In each of these figures a different cervix image is shown, along with boundaries marked by gynecologic oncologists. **Figure 3** is an enlarged view of one of these screens, where the color-coded boundary labels may be seen. For this particular image, the oncologist identified six different feature types: cervical borders, acetowhite lesion, squamous metaplasia, os (the opening into the uterus), squamo-columnar junction (SCJ), and mucus.
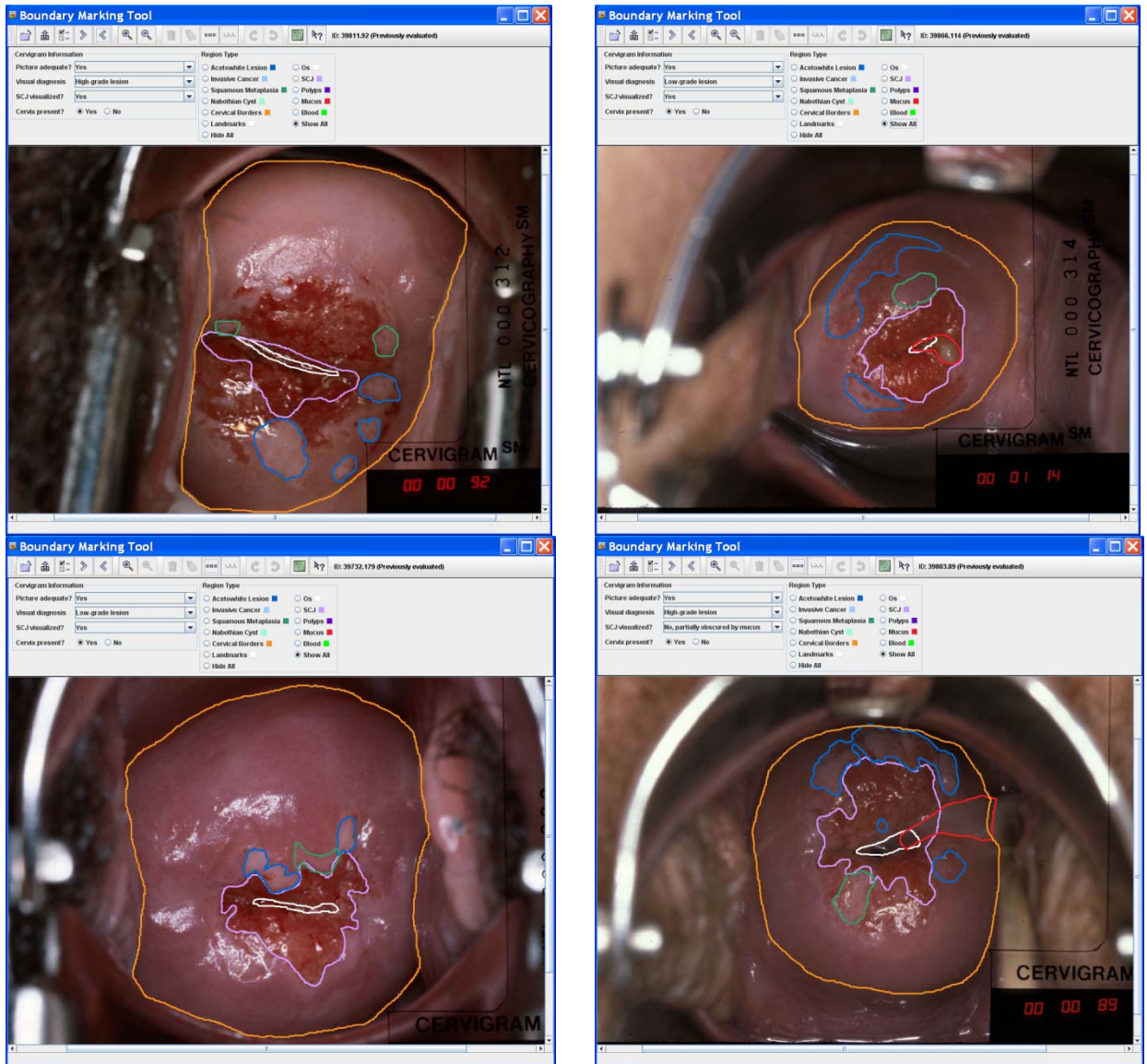
Figure 2 Examples of Boundary Marking Tool screens showing oncologist-marked boundaries on the uterine cervix.
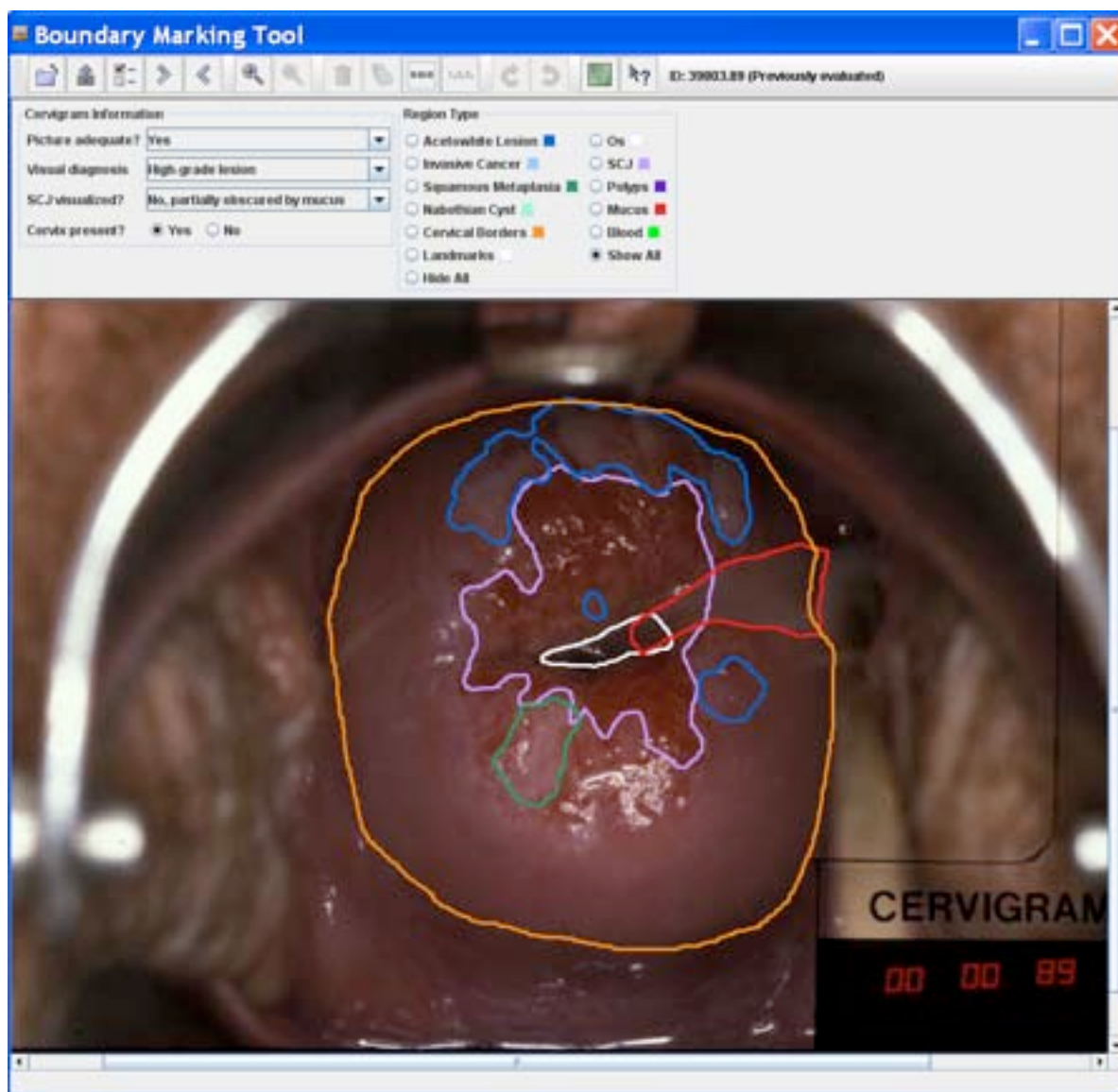
Figure 3 In this enlarged Boundary Marking Tool screen, the labels corresponding to the expert-identified regions may be read. For example, the violet boundary corresponds to the SCJ (squamo-columnar junction), which separates smooth, squamous tissue outside the boundary from rougher, columnar tissue inside the boundary.

4.1.2 Use

The first of the imaging tools to be developed, the BMT has been used in a number of uterine cervix studies by the National Cancer Institute. For examples of these studies, see Sections 5.1-3. It is currently installed not only on an NLM Communications Engineering Branch server, but also at an NCI contractor site, where it is operated independently of NLM for the National Cancer Institute's study currently taking place at the University of Oklahoma Health Sciences Center. (The contractor is responsible for various data processing services, including the archiving of the Guanacaste and ALTS data. The installation of the BMT at this site was the first

deployment of the BMT outside of the NLM environment and was a significant migration of our work from lab to operational use.)

The BMT has also been used outside the field of uterine cervix cancer: specifically, in a Phase II Clinical Trial to evaluate the effect of nicotine patch treatment on Kaposi sarcoma lesions. This work is described in Section 5.5. **Figure 4** shows the BMT screen as it was configured for this study.
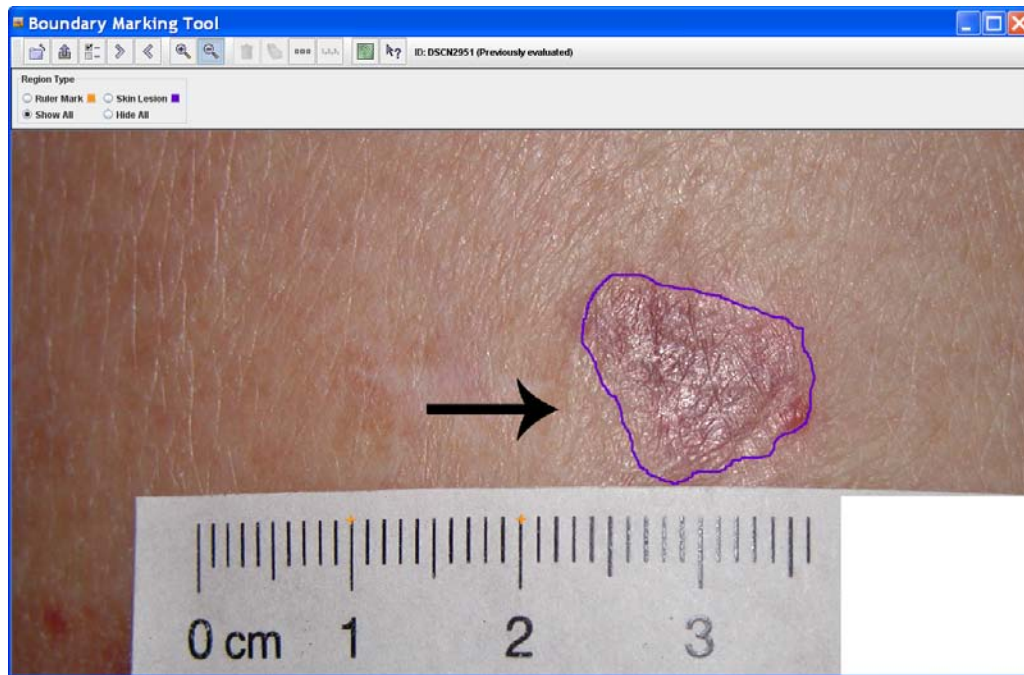
Figure 4 The Boundary Marking Tool was modified to collect data for a Phase II clinical trial of the effectiveness of nicotine patch treatment for Kaposi sarcoma (KS). Digital photographs of KS lesions were acquired at several time points over the course of the study. Medical experts marked lesion boundaries, and the lesion areas were computed from the digital images, using the ruler in the image to calibrate the physical measurements. The measured lesions areas were used to assess whether the sizes of lesions treated with nicotine regressed. (The study concluded that no statistically-significant regression was observed.)

4.1.3   Technology
The BMT is a Java client-server application that is distributed using Java Web Start. It may be used with either the MySQL or Postgres DBMS systems, and uses PHP on the server side. In addition it uses Apache Tomcat Java servlet technology.

4.2   **BMT Study Administration Tool (BSAT)**

4.2.1   Capability
The BMT Study Administration Tool creates and gathers results from *BMT studies*. Prior to the development of the BSAT, all BMT studies were created, and the results gathered, by an NLM computer scientist who used database management utilities to interact with the BMT databases.

The BSAT allows a *study administrator*, designated by the content specialists who design the study, to carry out these functions through a Web interface.
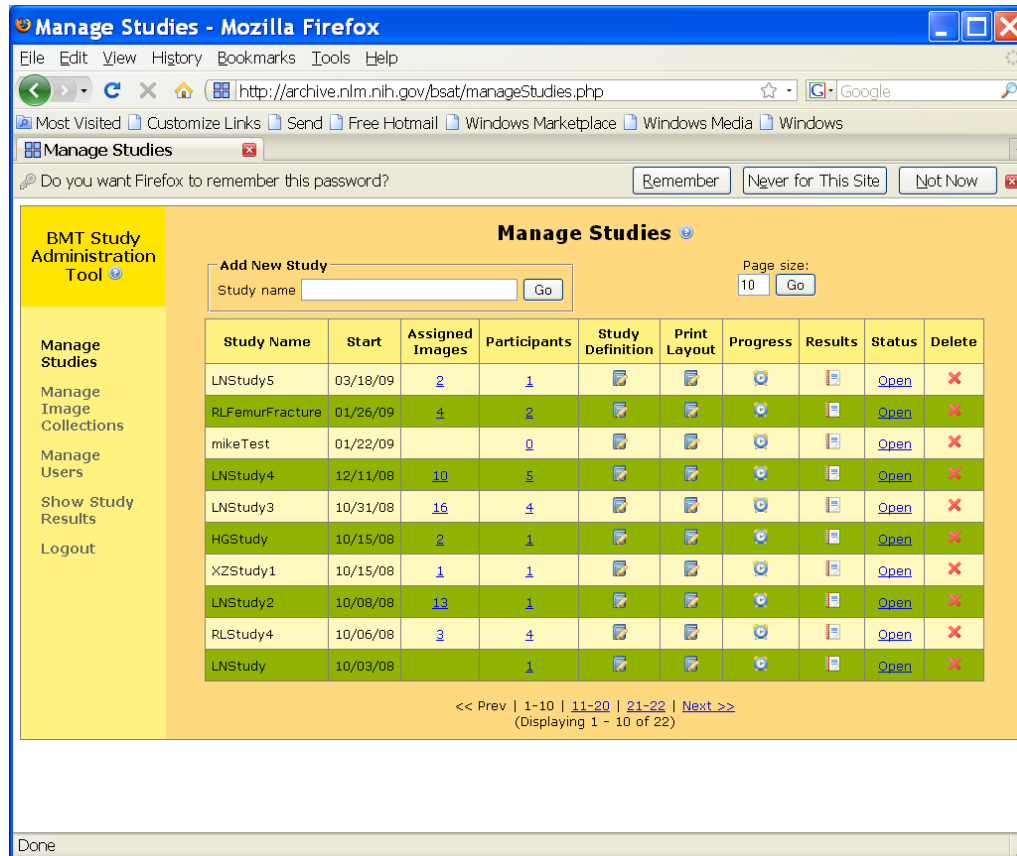
Figure 5 This figure shows the main screen from the BMT Study Administration Tool (BSAT). This tool allows a privileged user (the "study administrator") to define "studies" to be carried out with the BMT. Study definition includes (1) defining the specific images to use, (2) defining the specific global and region-specific data to be collected, (3) assigning observers to the study, and (4) viewing results. All of these functions may be done over the Web, using the BSAT.

The components of a BMT study and the associated BSAT capabilities are described below. A *BMT study* consists of the following:

- A set of images to be viewed for the study. The BSAT allows images to be uploaded by the study administrator to the BMT/BSAT server site. The study administrator may define named *image collections* to hold the uploaded images. Then, he/she may select images from one or more image collections for a specific study.

- Definition of data to be collected on the images. The BSAT allows the study administrator to define particular fields of data to be collected for an image in the study. The administrator may define these fields as being associated with the image as a whole, or with particular, named regions for which the user will draw boundaries during the study. Along with the boundary type to be drawn, the administrator may also specify characteristics of the boundaries, such as the color and width of the boundary, whether the boundary may be rotated, and whether multiple instances are allowed. The administrator

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may also define boundary-level flow control by specifying that for a particular boundary, the user may not proceed until descriptive items on a pop-up menu have been supplied.

- Assignment of observers for the study. The BSAT allows the study administrator to assign observers for the study from BMT users listed in the BSAT database. (A *user*, in this context, is anyone listed in the BSAT database login/password table; a user may log in to the BMT, but cannot access any particular study data until he/she has been assigned to that study; once a user is assigned to a specific study, he/she becomes an *observer* for that study and can access the study data.) The study administrator may also use the BSAT to add users to the BSAT database.

As soon as an administrator defines a study with the BSAT, the study is available through the BMT. When an observer for that study logs in to the BMT, the observer will be able to access the images defined for that study, and the BMT screen will be automatically configured with the correct graphical interface controls to allow the observer to enter the data, including drawing the boundaries on the image, for that study.

The BSAT study administrator may then use the BSAT to retrieve the study results that have been provided by the observers in the study. All BSAT and BMT operations take place over the Web. **Figure 5** shows the main screen (the *Manage Studies* screen) for the BSAT.

4.2.2   Use

The BSAT has been used by NCI researchers to configure the BMT for data collection in the NCI biopsy study now taking place at the University of Oklahoma Health Sciences Center.

4.2.3   Technology

The BSAT is a client-server Java application distributed with Java Web start. It uses Apache Server and Apache Tomcat Java servlet technology. It may use either the MySQL or Postgres DBMS systems. On the server side, it uses PHP, and it uses Orbeon Forms for providing the client interface that lets the user define the layout of BMT screens.

4.3   **Multimedia Database Tool (MDT)**

4.3.1   Capability

The MDT is a Web-based database system for text/image databases and provides access to the 60,000 digitized cervigram images collected in the NCI Guanacaste 7-year longitudinal study, along with PAP test results, histology results, and HPV virus test results for individual HPV virus types; the MDT also provides access to the 40,000 digitized cervigram images collected in the NCI ALTS 2-year longitudinal study, along with the data (similar to that of Guanacaste) that was collected. To generalize beyond its current uses, the MDT is designed with an abstract data model that is intended to allow the incorporation of new text/image databases without alteration of the MDT software. **Figure 6** shows a typical results screen for the MDT.
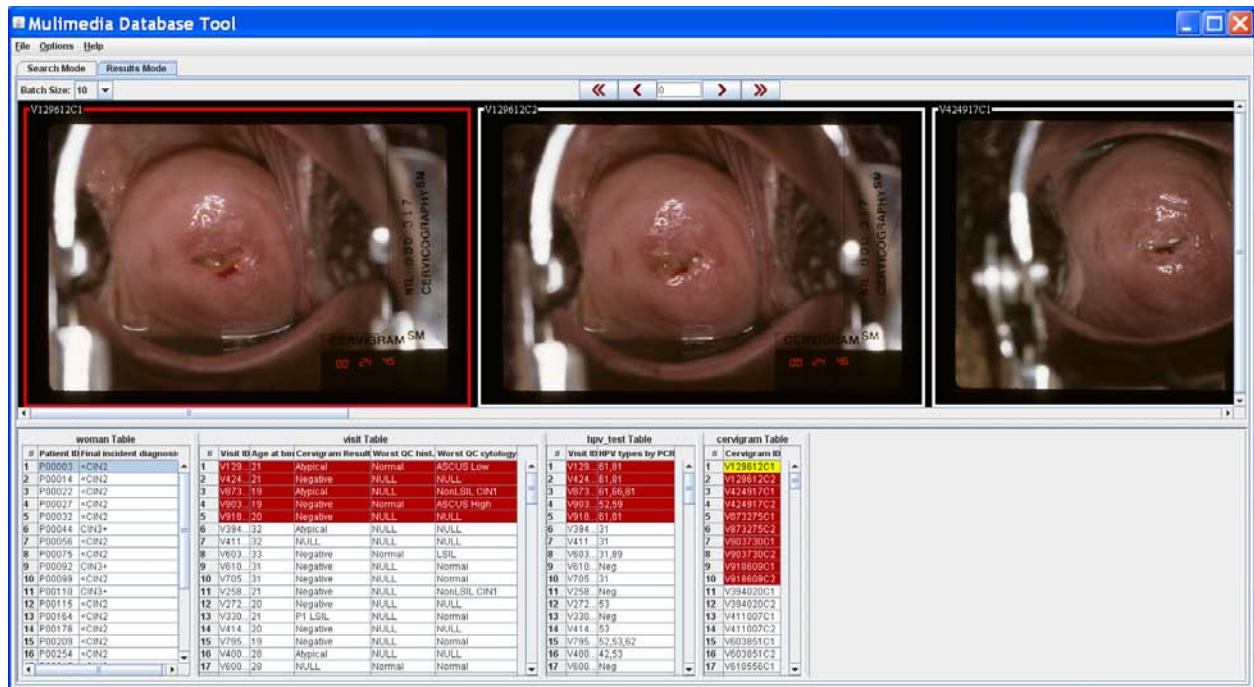
Figure 6 This figure shows a typical results screen for the Multimedia Database Tool (MDT). At left is the Patient Table, which lists the (de-identified) Patient IDs. Much of the clinical data is given in the Visit Table (second from left.) The two tables at the right list identifiers for images. When a particular field is selected with a mouse click, all of the related fields in the other tables are highlighted in color. In this example, all of the data related to the first patient is highlighted. Graphical mark-up collected with the Boundary Marking Tool may also be displayed in the MDT.

4.3.2   Use

The MDT is used by NCI researchers to select data for use in studies carried out with the Boundary Marking Tool and to store results from BMT studies. Also, academic collaborators at Lehigh University use it to retrieve histology diagnoses associated with particular images for research into automated training systems.

4.3.3   Technology

The MDT is a client-server Java application distributed with Java Web Start. It uses Apache Server and Apache Tomcat Java servlet technology. It may be used with either the MySQL or Postgres DBMS systems. For deployment it uses Apache Ant, Java, Groovy, and (for debugging) Netbeans.

4.4   **Virtual Microscope (VM)**

4.4.1   Capability

The Virtual Microscope allows digitized histology images to be viewed over the Web, and data such as diagnostic interpretations to be recorded into a central database. It incorporates capability to deliver large images in *tiled* form (i.e., the image is divided into many smaller subimages or *tiles*) over the Web in such a way that the user receives only the image data

required to construct the image defined by the user's current zoom and pan level, and to locally cache the tiles that have been previously sent to the user's computer. In this way, the viewing of these very large images (a histology image may exceed 40,000 x 70,000 pixels, i.e. more than 8 GB uncompressed, for example) becomes feasible over the Web. It has capability (similar to that of the BSAT, for the BMT) to allow a study administrator to define a VM study, and incorporates the notion of constrained vocabulary for diagnostic purposes. (The current vocabulary within the VM consists of the W.H.O. classifications for diagnoses of lung cancer. The W.H.O. vocabulary was incorporated to meet the needs of a specific study we are conducting in collaboration with the NCI Genetic Epidemiology Branch.) **Figure 7** and **Figure 8** show some of the main screens of the Virtual Microscope.

4.4.2   Use
The VM has been used in two internal studies by NCI with uterine cervix histology images, and is now being used in a study to compare glass slide versus virtual microscope diagnoses for lung cancer images.

4.4.3   Technology
The VM is a custom-written, Java client-server application, which does not rely on commercial software. It operates with a JIIP (Java Internet Imaging Protocol) server and uses the Akelos framework (like Ruby on Rails, but for PHP) for the study administration components.
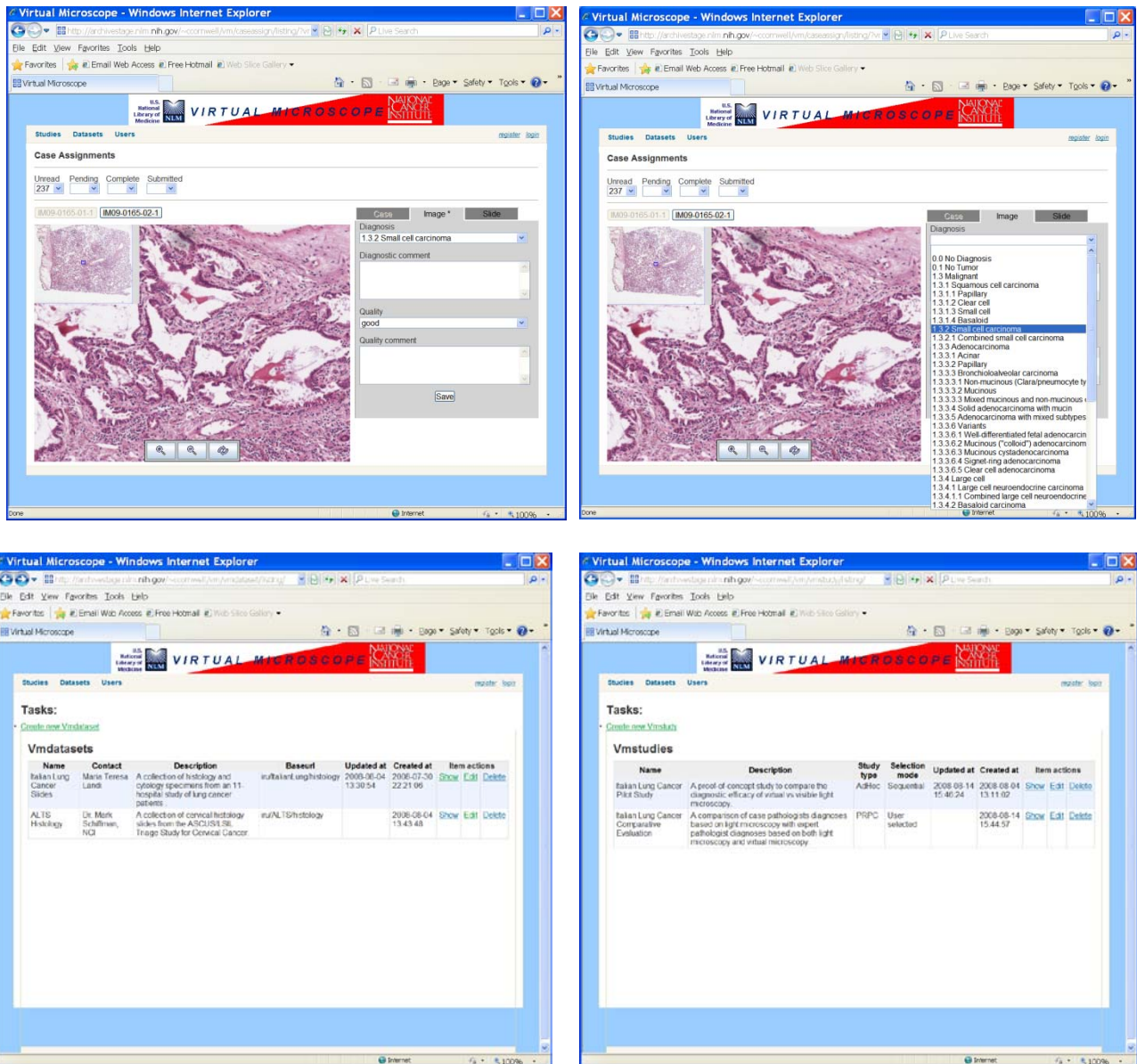
Figure 7 This figure shows screens from the Virtual Microscope. In the upper left, the main screen shows the image area with a small inset navigation image. Controls for recording diagnostic interpretation are in the right-hand part of this screen. In the upper right, the drop-down menu of controlled vocabulary terms for diagnosis is shown. The VM allows a privileged user to create new studies and to add new image datasets to be used. Screens to carry out these functions are shown in the lower left and right, respectively. An additional screen (not shown) allows new users to be added to the system.
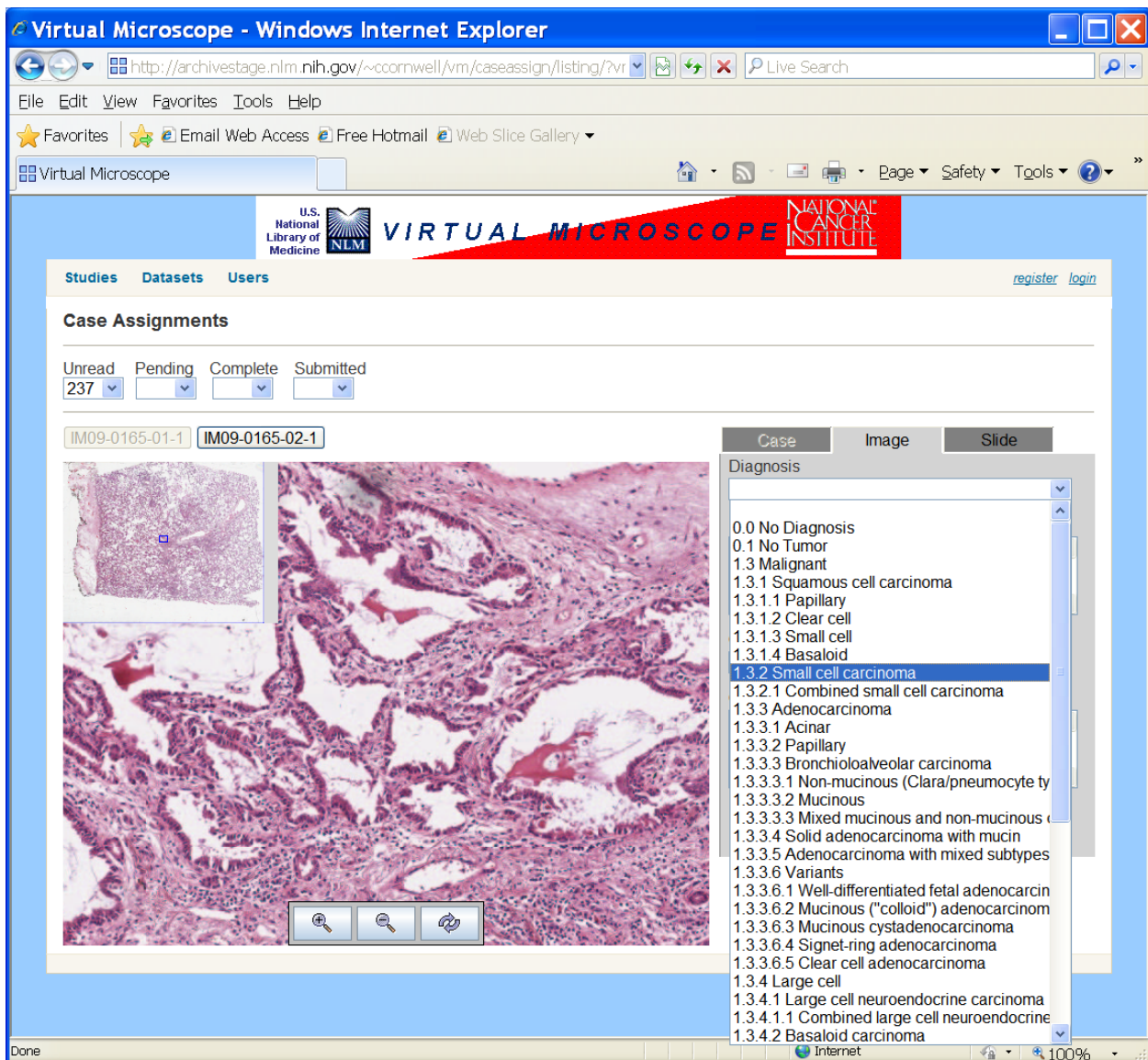
Figure 8 This is an expanded view of the upper-right image in Figure 7 and illustrates the World Health Organization controlled vocabulary that is incorporated in the VM for an ongoing lung image study with NCI.

4.5   **Teaching Tool (TT)**

4.5.1   *Capability*

Systematic testing and knowledge assessment are required by many professional bodies. This task may be difficult when the subject matter has a large visual component. The Teaching Tool provides the capability for image-based knowledge testing over the Web. It allows exam content to be defined in the form of *pools* of questions which are logically associated (for example, questions about the clinical management of adolescent girls who are HPV positive). At run time, the Teaching Tool makes random draws from these pools according to the exam definition and sequentially presents the questions (including any associated images) to the user's (i.e., the *testee's*) screen; user responses are collected in the form of answers to multiple choice questions and as mouse clicks on particular points in the image. (The placing of the mouse may indicate,

for example, the user's selection of a point on the image as a biopsy site.) A particular pool category is the case pool which consists of three individual questions for a particular patient: *diagnosis*, *biopsy site selection*, and *management*.

The Teaching Tool provides level-of-access control and divides *users* (in this context, the generic name for anyone with a login/password in the Teaching Tool database) into *administrators*, *program directors*, and *testees*.

Administrators may add users, assign exams, reset exams to allow retakes, view results, and edit user descriptive information. When an administrator assigns an exam to a particular user, the Teaching Tool automatically notifies the user by e-mail, sends a unique exam code for that particular exam, and enables a graphical control on that user's login screen that allows him/her to access the *Begin Exam* page.

Program directors are experts at medical institutions who supervise training of medical residents over a multi-year period. They may edit a testee list to add or remove testees at their particular institutions and may monitor the progress of students over their multi-year training.

Testees may access and take the exams they have been assigned. (Only users with a valid login/password and exam code may take a particular exam). Other functions of the Teaching Tool include enforcement of timing constraints for the exams, practice test administration and automatic exam grading. The Teaching Tool database is currently configured to administer the American Society for Colposcopy and Cervical Pathology (ASCCP) *Colposcopy Mentorship Program* (CMP) exam and the ASCCP *Resident's Online Exam* (ROE). Example screens from the Teaching Tool are shown in **Figure 9**, **Figure 10**, and **Figure 11**.
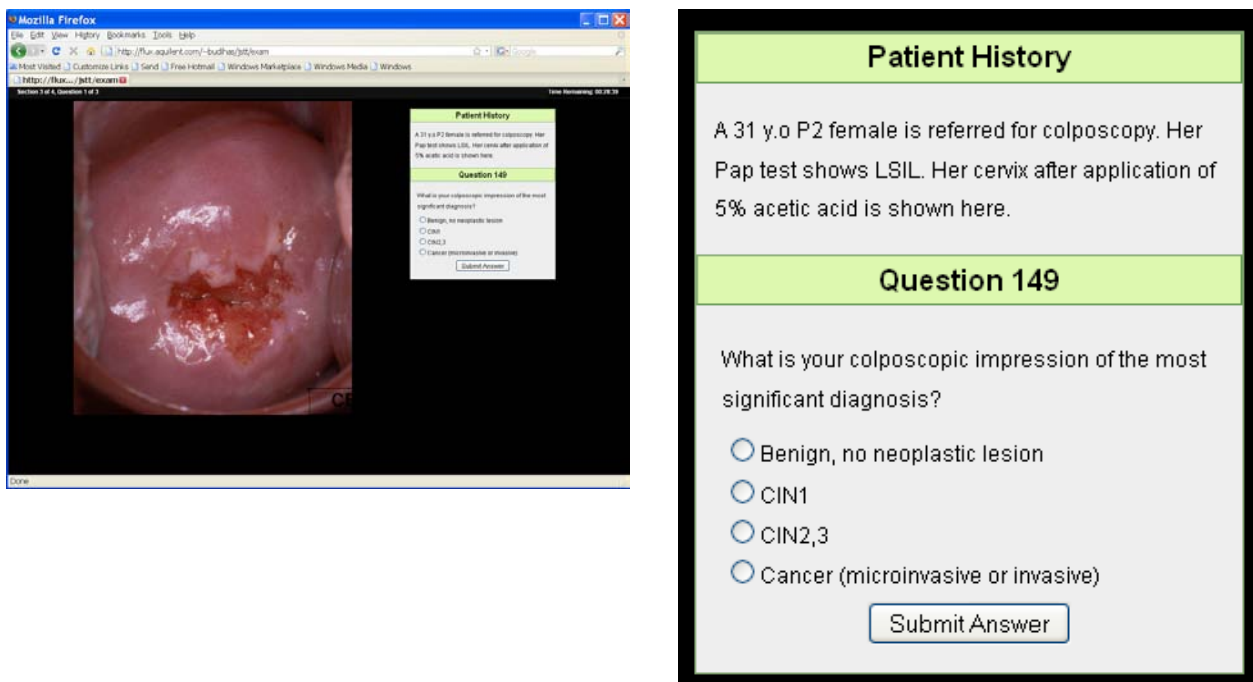
Figure 9 A Diagnosis Question for one case in the Teaching Tool. The screen text is shown in expanded view at the right.

Figure 10 The Biopsy Question for the above case. The testee clicks to place a crosshair at the spot the testee would take a biopsy. Acceptable regions for correct biopsy were created by consensus of multiple gynecologist oncologists, using data collected with the Boundary Marking Tool.
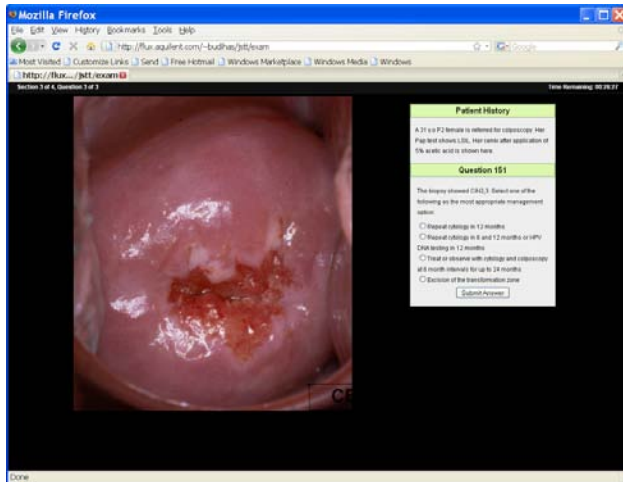
Figure 11 The Management Question for the above case. Management is scored according to the most recent management guidelines of the American Society for Colposcopy and Cervical Pathology.

4.5.2   Use

The Teaching Tool has now completed two beta tests for the CMP. More details of these tests are given in Section 6. Since the ASCCP has acquired an operational server and the Teaching Tool has been installed, they are expected to begin operational use of the tool from that site for the Colposcopy Mentorship Program exam in the near future.

4.5.3   Technology

The Teaching Tool operates in a standard Web browser and uses Javascript and AJAX. On the server side, it uses PHP and the MySQL or the Postgres DBMS system.

4.6   Visual Triage Study Tool

4.6.1   Capability

The Visual Triage Study Tool is built upon Teaching Tool technology, but modified and adapted for the special requirements of the NCI Visual Triage Study. It provides image and text display, collection of user responses to multiple choice image-based questions, and database storage of the collected information, for both an "expert" phase used to create "ground truth"; and for an "observer" phase where data is collected from non-experts (which is later evaluated off-line

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against the expert "ground truth"). The specific phases and use of the system in the NCI Visual Triage Study are described below and in Section 5.4.
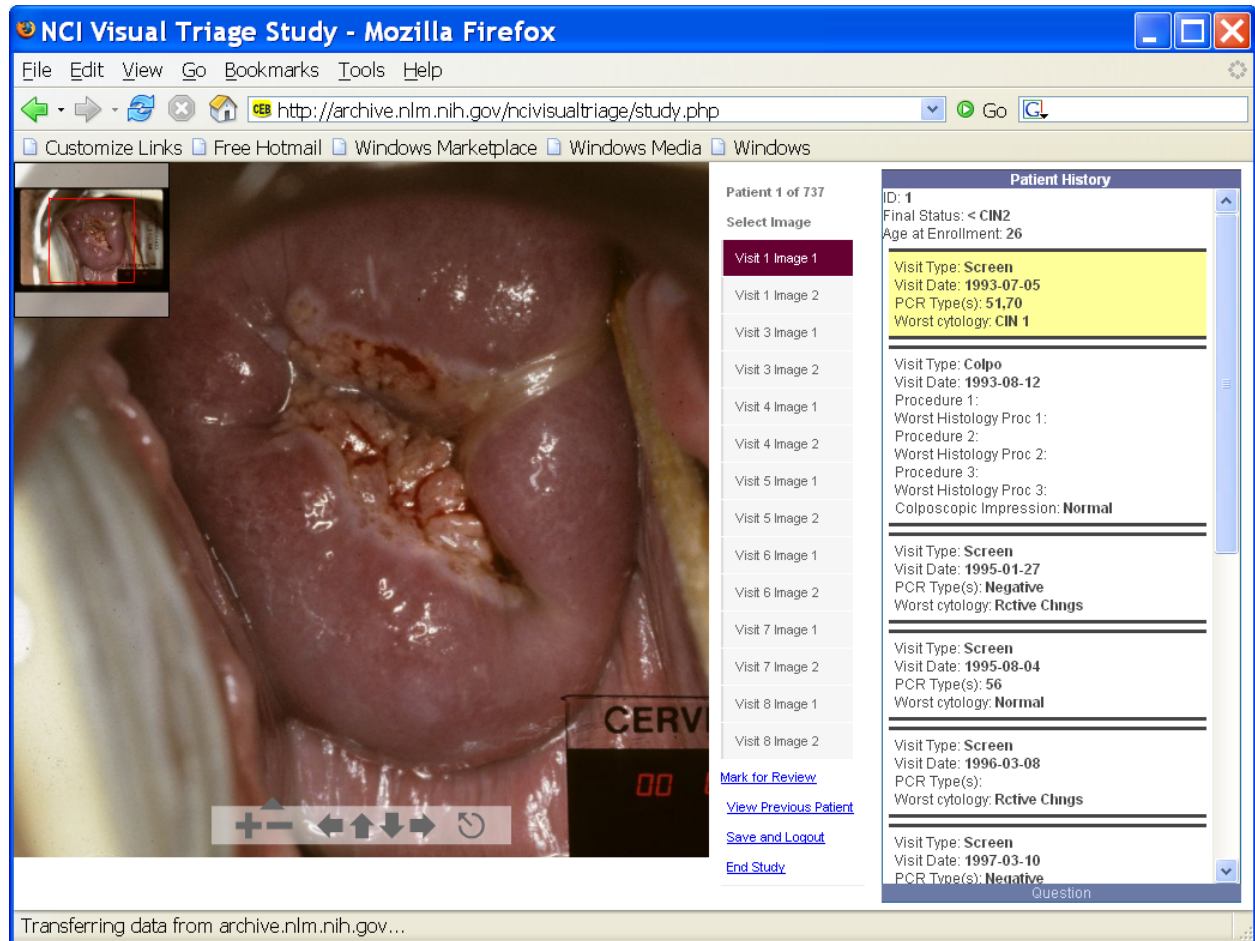
Figure 12 This figure shows a screen from Phase 1 of the Virtual Triage Study (VTS), using the VTS Tool. In this phase, experts reviewed 739 images of the uterine cervix and evaluated each HPV-positive patient as treatable or not treatable by cryotherapy. In Phase 2, these same images were evaluated by gynecologist oncologists to assess the feasibility of screening for treatment by non-expert health workers. In this example, all of the data related to the first patient is highlighted.

4.6.2 Use

This tool was used to investigate the capability of non-oncologist health workers to screen HPV-positive women for treatability by cryotherapy. This work had two phases and is described in detail in Section 5.4. In the first phase, expert oncologists determined "truth" judgments for evaluating performance of the non-experts. In the second phase, the non-experts carried out a simulated patient screening, using cervix images displayed by the Visual Triage Study Tool. Screen shots from phases 1 and 2 of the study are shown in **Figure 12** and **Figure 13**, respectively. The non-oncologist participants in phase two were midwives in the towns of Moyobamba and Tarapoto, Peru. See **Figure 14**.
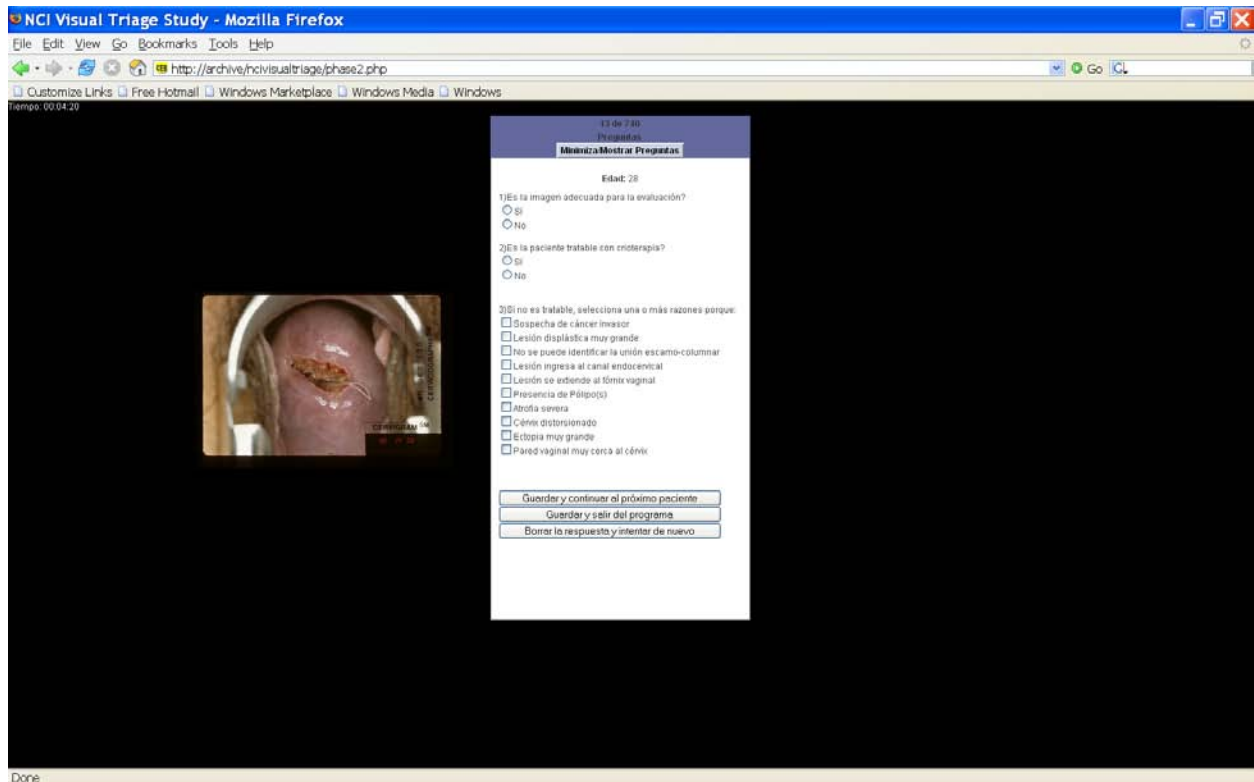
Figure 13 This figure shows a screen from Phase 2 of the Virtual Triage Study (VTS), using the VTS Tool developed by CEB. In this phase, the non-experts reviewed 739 images of the uterine cervix and evaluated each HPV-positive patient as treatable or not treatable by cryotherapy. The monitors used by the non-experts were heterogeneous with respect to make and model; CEB engineers adjusted the image data for each particular monitor type, in order to make the images have approximately the same physical size, to simulate viewing the cervix through a colposcope. The screen dialogues were translated by Spanish speakers at NCI.

Figure 14 The review of the Visual Triage images by the non-expert observers took place in Moyobamba and Tarapoto, Peru (top). Much of the work was done in Internet cafes (lower left); the non-experts were Peruvian midwives (lower right, front row) who were given a short course in visual screening by Dr. Jose Jeronimo, then of NCI.

4.6.3   *Technology*

The Visual Triage Software Tool is Web browser-based and uses Javascript and AJAX. On the server side, it uses PHP and the MySQL DBMS.

4.7   Inflammatory Breast Cancer (IBC) Tool

4.7.1   Capability

The Inflammatory Breast Cancer Tool allows the display of digitized photographs of the breast and the collection of diagnostic information pertaining to this disease. A screen shot from the Inflammatory Breast Cancer Tool is shown in **Figure 15**.
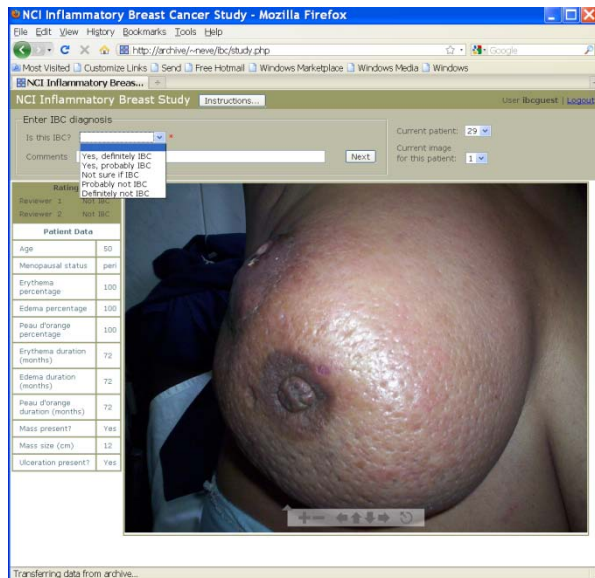
Figure 15 The Inflammatory Breast Cancer Tool allows expert review of digitized photographs of breast anatomy for patients who have been diagnosed in the field with Inflammatory Breast Cancer. This study is currently underway and patient data is planned for collection in Egypt, Tunisia, Algeria, and Morocco.

4.7.2   Use

This tool is currently being used in a study of the risk factors for Inflammatory Breast Cancer, and data is being collected from sites in Egypt, Tunisia, Algeria, and Morocco. See Section 5.7 for a detailed description of this work.

4.7.3   Technology

The IBC Tool is Web browser-based and uses PHP and the MySQL DBMS system on the server side.

4.8   HPV Linear Array Tool

4.8.1   Capability

The identification of specific types of HPV infecting a patient is of significant clinical importance. To this end, we have developed an HPV Linear Array Tool that automatically segments HPV linear array images to identify specific patient *strips* on the images and specific, rectangular *cells* that correspond to signals associated with particular types of HPV virus. After segmentation, the tool computes detected signal strength in each cell by finding the mean value

of the pixel gray levels within that cell. This is the *absolute signal* strength. The tool further estimates the noise floor level across the strip corresponding to a single patient, and subtracts this noise floor from the absolute signal, to obtain a *relative signal* or "true signal" strength. These measurements (absolute and relative signal strengths) are automatically output in the form of an Excel spreadsheet. **Figure 16** shows an HPV linear array image with 20 strips (18 patient strips and two test strips.) **Figure 17** shows the correspondence between rectangular cells in the strips with particular HPV types. **Figure 18** is a graph of the signal responses down one representative strip (which corresponds to one patient). These detected responses are output by the algorithm built into the HPV Linear Array Tool.
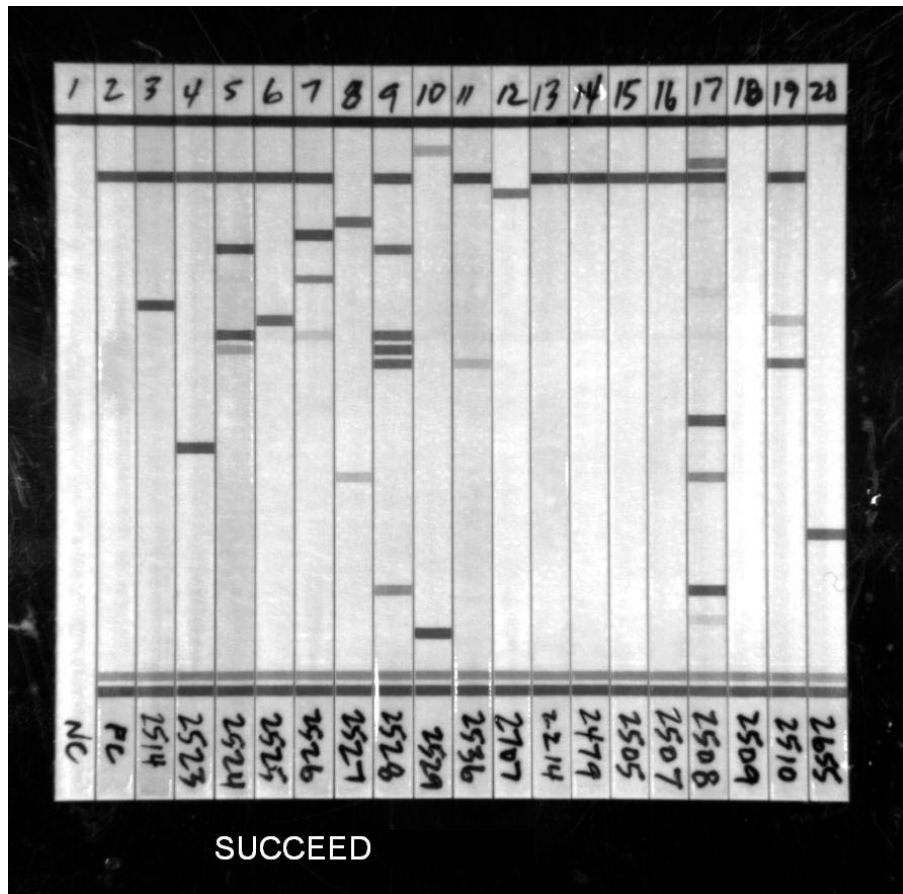
Figure 16. This figure shows an HPV Linear Array image, composed of vertical HPV Linear Array strips. One strip corresponds to a single patient. (The strips labeled "NC" and "PC" are test strips.) Each strip may detect up to 37 individual types of HPV. The rectangular areas that stand out from the background correspond to detected responses for particular HPV types. The intensity of the response is measured by the darkness of the rectangular area.

4.8.2 Use

The HPV Linear Array Tool has been used by NCI to study the correlation of human (visual) interpretation of HPV linear array data with machine interpretation

The HPV Linear Array Tool is a MATLAB application which incorporates customized algorithms for segmenting individual linear array strips from an image containing from 12 to 20 such strips, identifying the rectangular regions that correspond to specific HPV types within a strip, estimating the background noise within the strip, and computing the signal strength of each HPV type, relative to the background noise.
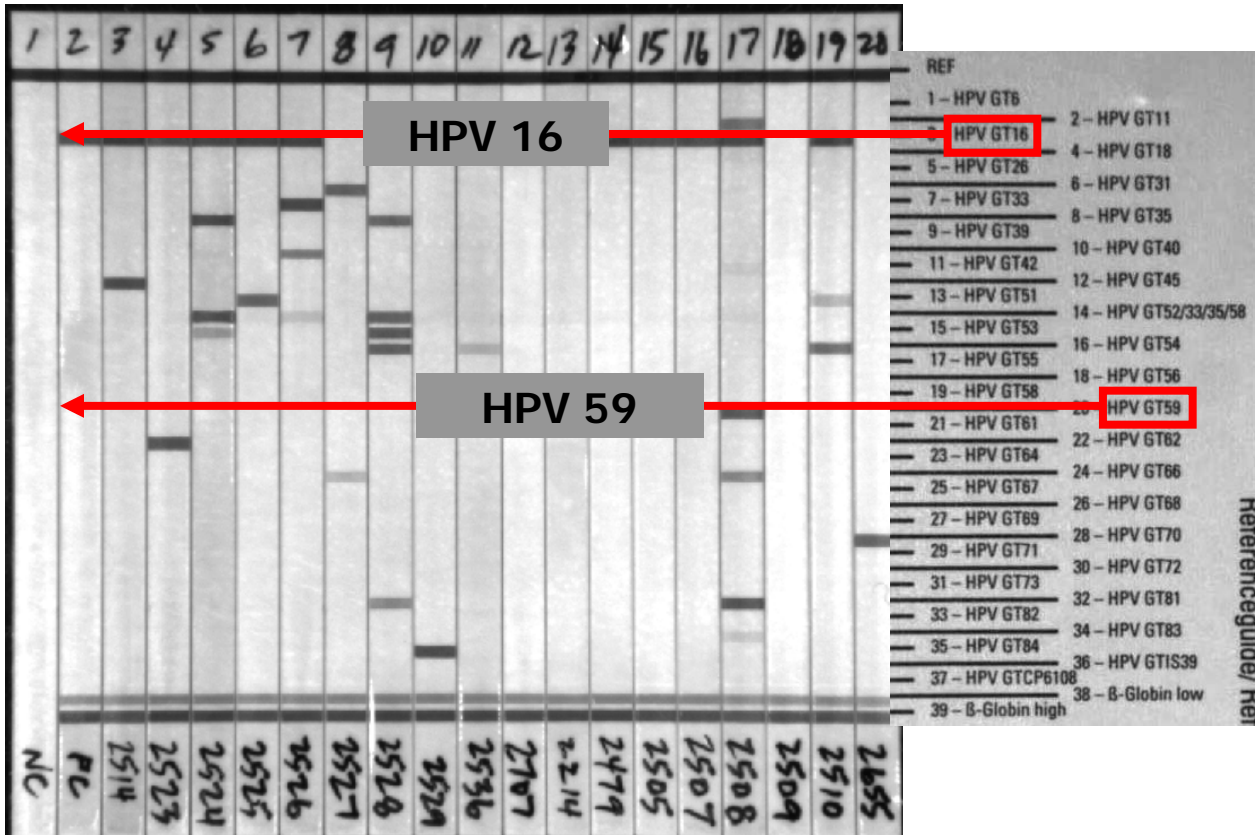
Figure 17 In this figure, the key to the HPV virus types has been placed to the right of the Linear Array image. All rectangles at the same vertical level correspond to the same HPV type. Example levels for HPV 16 and HPV 59 are shown.
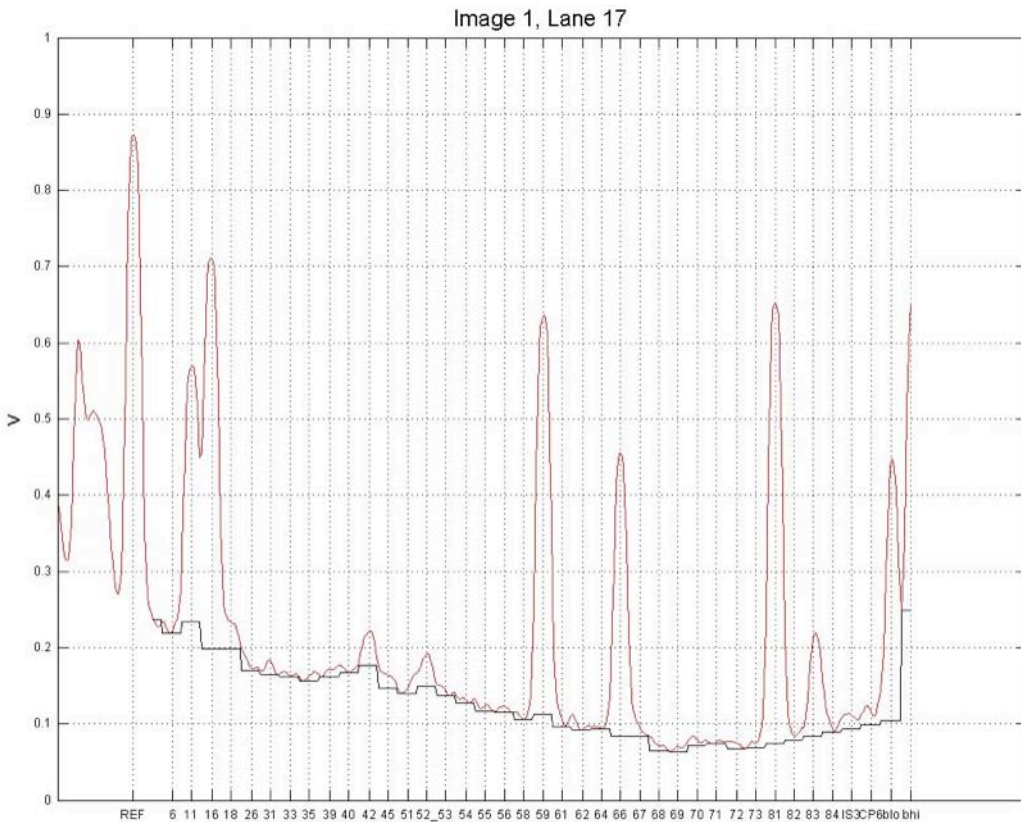
Figure 18 The HPV Linear Array Tool analyzes the signal responses in each "lane" (one lane = one patient) of a Linear Array Image and outputs the signal strength above background. The graph above shows a plot of the signal strength for patient 17 of the image in the previous figures. The lane for this patient has been cut from the image and is superimposed on the graph. The black, piecewise-linear line is the estimated noise background down the lane. Signal strength is measured relative to this background. For this patient, HPV signals can be seen for types 16, 18, 42, 52_53, 59, 66, 81, and 83.

5 Impact of the tools in cancer research

The tools described in the previous section are the result of collaborative work among the Communications Engineering Branch, researchers in four different branches of the National Cancer Institute, and the American Society for Colposcopy and Cervical Pathology. They are intended to address problems of high significance for uterine cervix cancer screening and training of medical professionals in the field of colposcopy. Beyond these primary objectives, the work has wider applicability: for the storage of a broad spectrum of medical image types, along with descriptive biomedical information collected from patients or research subjects; the retrieval of this information over the Internet; the collection and dissemination of image region-based information, such as biopsy sites or potential pathological areas as evaluated by visual screening; and proficiency evaluations of medical professionals using image-based testing.

This collaborative effort has had an influence, and continues to do so, on efforts toward the detection and prevention of cervical and other cancers in multiple ways, as described below.

5.1 Biopsy protocol for pre-cancer/cancer detection.

A significant issue in cervix cancer diagnosis was identified by NCI in 2006 [10], based on data collected for 408 patients in the two-year ALTS study (see Section 1 for a description of ALTS). Using this data, NCI researchers concluded that colposcopy-guided biopsies only detected approximately two-thirds of high-grade pre-cancer or cancer, and that detection was better in the cases where more than one biopsy was taken, suggesting that multiple biopsies should be routinely taken to increase detection sensitivity of this severe pathology. This issue was elaborated in another 2006 NCI paper [6]:

> …the accumulated data suggest very strongly that the heart of colposcopic practice is the identification of the most abnormal area for biopsy. Because colposcopic appearance is often complex, and the most abnormal area may be small, the sensitivity of the procedure will depend on taking more than a single biopsy in many cases.

This paper provided an overall view of critical issues in the practice of colposcopy and referenced our work at the National Library of Medicine, in collaboration with NCI and the American Society for Colposcopy and Cervical Pathology, in contributing to the effort to make colposcopy "more robust, reliable, and sensitive within a few years".

An NCI effort is now underway, using our software tools, to collect biopsy data, which will, for the first time to our knowledge, create a large database to study the correlation of biopsy results with specific spatial data defining the sites on the cervix where the biopsies are taken. In this work, which has begun at the University of Oklahoma Health Sciences Center, data will be collected over a two-year period from 1,000 women who undergo colposcopic examination. During the exam, the colposcopist takes multiple biopsies; a digital image of the cervix is captured, and the colposcopist uses the Boundary Marking Tool to mark the biopsy sites on the image. The data is transmitted to NCI for analysis and will be made available as a database in the Multimedia Database Tool.

Additional data for this study, following the same protocol, will be collected from sites in Nigeria and in Costa Rica.

5.2 Capabilities and limitations of visual evaluations of cervix images and the implications for colposcopic practice.

Using 939 cervigrams from the 40,000 ALTS images digitized by NLM, a study was conducted to understand the correlation between HPV infection and visual appearance of the cervix. The Boundary Marking Tool was used by 20 colposcopists, selected by national leaders in colposcopy, to mark acetowhite lesion boundaries and to provide diagnostic evaluations of each image. Actual HPV infection status was known for each patient from the clinical data collected in ALTS, and it was possible to study the statistical relationship between the colposcopist diagnosis and the HPV status. The authors of the resulting paper [11] commented:

> To our knowledge, this is the first study to explore systematically the relationship between type-specific HPV infection and visual changes of the uterine cervix. HPV infection is the necessary cause of

cervical cancer, and we had hypothesized that colposcopic impression at the most basic level (lesion vs no lesion) would be associated strongly with molecular evidence of infection.

…

Based on our results, we suggest that this correlation does not exist; even when we evaluated the results as simple dichotomies (presence or absence of lesion vs presence or absence of HPV). A possible explanation for this finding is that not all the HPV infections are associated with visual changes of the epithelium. It is still not clear whether this lack of association is that some acetowhite lesions could be located out of the reach of the visual evaluation (endocervix) or that human papillomavirus produces no detectable alterations of the squamous epithelium in a subgroup of subjects.

The authors concluded that, with the exception of HPV16, the association of visual diagnosis with HPV infection is weak. The clinical implications are that HPV16 infections may be easier to detect during colposcopic examination, while infections due to other carcinogenic HPV types may be easier to miss. A further implication is that, as the prevalence of HPV16 decreases due to vaccination programs in the future, the performance of colposcopy for detection of lesions due to HPV may be altered.

The graphical (boundaries of the acetowhite lesions) and diagnostic data collected in this study will be put into the ALTS database of the Multimedia Database Tool.

5.3 Interobserver agreement in the evaluation of digitized cervix images.

Using the same data referenced above, acquired with the Boundary Marking Tool to study the relationship between HPV type and visual diagnosis, the *interobserver variability in diagnosis* among the 20 colposcopists was analyzed. Twenty of the 939 cervigrams were given a visual diagnosis by all 20 observers (i.e., the colposcopists); the remaining 919 cervigrams were assigned to the 20 observers so that each image was given a visual diagnosis by two observers, with each observer evaluating 112 of the 919 images. For each image in the 919, the agreement in diagnosis between the two observers for that image was analyzed. It was found that pairs of colposcopists agreed in diagnosis for only 57% of the images. This finding was confirmed by analysis of agreement using the 20 images that all 20 observers evaluated. The authors of the resulting publication [12] concluded:

Colposcopic diagnosis using static images is poorly reproducible and might reflect similar problems in practice.

See also [13] for further published analysis of this data.

5.4 Evaluation of the feasibility of non-expert health workers to screen for cryotherapy treatment for HPV infection.

Treatment by cryotherapy has been proposed for HPV-infected women in developing countries. However, this treatment is not feasible under certain conditions of the cervix, including the presence of invasive cancer, polyps, large dysplastic lesions, atrophy, and severe distortions of the cervix anatomy. Visual screening is required to inspect for these conditions that would make treatment by cryotherapy not acceptable. It would be a great advantage if this visual triage could be carried out by health workers other than highly-skilled medical experts, such as gynecologic

oncologists. To evaluate the feasibility of such a visual triage program, NCI conducted a study in Peru, using 522 cervigram images from the NCI Guanacaste study to simulate cervix viewing. Twelve midwives from the Peruvian towns of Moyobamba and Tarapoto participated as non-expert screeners and were given on-site training in screening procedures by NCI experts. Five gynecologists also participated as screeners to provide comparative results to the midwives.

Using the data collected in the Guanacaste study, patients were judged as needing treatment if they had a histologic diagnosis of cervical intraepithelial neoplasia of grade 2 (CIN2) or worse; or if they had 5-year persistence of carcinogenic HPV. Two lead gynecologists, independently of the five gynecologist screeners, determined "truth" for treatability, by viewing the images in advance and classifying them as "treatable" or "not treatable". A simulated screening scenario was created in which the screeners viewed the digitized images of the cervix and answered an on-screen questionnaire to provide assessment of treatability for cryotherapy, based on visual appearance of the cervix. Images and the questionnaire were displayed using the NLM-developed Visual Triage Study software, and the study was supported by e-mail and telephone contact between the NCI on-site experts in Peru and NLM engineers.

Much of the simulated screening work was done in Internet cafes at the Peruvian locations. The technical work included adjusting the image data so that it displayed with the same physical size across the variety of monitors that were available; this size was chosen to mimic the appearance of the cervix when viewed through a colposcope.

The study results showed that the midwives and five screening gynecologists correctly identified about 58% and 64%, respectively, of the women judged not treatable by the lead gynecologists. The proportion of women judged not treatable was highly variable across the screeners, and ranged from about 19% to 61%, and interrater agreement was poor, with mean pairwise overall agreement of 71% and 66% for midwives and gynecologists, respectively. From this study, NCI concluded [**14, 15**] that the suboptimal performance of visual triage suggests that screen-and-treat programs for treating precancerous lesions may be insufficient for treating precancerous lesions, although improved, low-technology triage and/or treatment options are needed. This work provided the data for a successful Ph.D. dissertation in epidemiology from the Johns Hopkins University Bloomberg School of Public Health in 2008 [**16**].

5.5   **Treatment of Kaposi sarcoma by nicotine patch.**

Researchers in the NCI's Viral Epidemiology Branch investigated a treatment for classic Kaposi sarcoma (cKS), a malignancy of dermal endothelial cells that is caused by human herpes virus 8 (HHV8) infection, using the NLM-developed Boundary Marking Tool. Cigarette smoking is associated with a fourfold lower risk of cKS. It is also known that cKS is highly sensitive to perturbations of immunity and that nicotine induces alterations of immunity that could be relevant to dermal cKS; specifically, nicotine affects the functions of dendritic cells and the production of interferon gamma. In addition, it is possible that the vasoconstrictive effects of nicotine might counteract the vascularity of cKS lesions. These considerations led NCI to hypothesize that treatment of cKS with nicotine dermal patches would induce regression of cKS

lesions. The study subjects were 24 patients, each of whom had at least three cKS lesions; for each patient, three lesions were randomly treated with a dermal nicotine patch, a placebo patch, or no patch, over a period of 15 weeks. Digital photographs of the lesions, including a calibration ruler, were taken at seven time points during the 15 weeks. These images were uploaded to the Boundary Marking Tool, and two NCI experts used this tool to circumscribe the lesions and to manually mark two points on the rule in the image which corresponded to a one centimeter length. The number of image pixels between the two marked points was used to convert image pixel measurements to physical measurements and to compute the physical area of a lesion, based on the number of pixels within the lesion boundary marked by the experts. The study did not detect statistically-significant changes in the lesions areas across the different treatments (nicotine, placebo, none) [**17**]. The investigators hypothesized that nicotine might inhibit cKS development but not affect its progression. Alternatively, the observation period of the study may have been too short or the lesions too advanced (most were thick nodules that had been present for months or years) to detect regression.

5.6   **Virtual Microscope vs. Physical Microscope Diagnoses for Lung Cancer.**

The NCI Genetic Epidemiology Branch is studying cancer-related diagnoses from lung histology images that are made using glass slides compared with diagnoses for the same images that are made with the NLM-developed Virtual Microscope. The goal is to archive images of interesting tumors for which data on gene expression, microRNA expression, methylation, protein patterns and sequencing are available or planned. The images will also constitute an educational tool for medical students. Two sets of histology image data for the study have been provided to NCI by medical collaborators in Italy, the first comprising 150 glass slides from lung cancer cases, and the second comprising 79 glass slides of lung tumors with bronchioalveolar features; these have been digitized by NCI/NLM. In addition, pathology reports for the histology have been made available by the Italian collaborators. Those reports have been deidentified and imported into the VM database. Review of diagnoses for both sets of physical slides was made by Dr. Ilona Linnoila of NCI's Center for Cancer Research at the NIH Clinical Center. Dr. Linnoila's diagnoses for a subset of the digitized slides have also been recorded, and both sets of diagnoses cross-matched with those of the Italian pathologists. Work is in progress to resolve scanning artifact issues on a few of the images to allow completion of the study.

5.7   **Case-control study of Inflammatory Breast Cancer**

The NCI Biostatistics Branch is conducting a study of the risk factors for Inflammatory Breast Cancer (IBC) that is focused on patients in North Africa, where IBC accounts for 6% of all breast cancers, and in one center in Marseilles, France, which has many North African immigrants. Inflammatory Breast Cancer is a rare, poorly understood and particularly aggressive form of breast cancer characterized by diffuse erythema and edema (redness and fluid accumulation beneath the skin) involving the majority of the breast. It is the most lethal form of breast cancer, with a median survival of less than four years, even with multimodality therapy and, to date, there have been no case-control studies of the etiology of IBC. In this work 400 IBC cases and non-IBC control cases will be identified at the collection sites in North Africa

and France. Digital photographs of the breast will be obtained and reviewed by at least one expert not involved in the data collection, using the NLM-developed Inflammatory Breast Cancer Tool. This NCI study is being carried out in collaboration with the International Agency for Research on Cancer, the International Breast Cancer Research Foundation, the World Health Organization, the University of Michigan, the University of Wisconsin, and cancer institutes and medical centers in Egypt, Tunisia, Algeria, Morocco, and France. Recruitment for this study started in Egypt in March 2009, and image collection has begun [**18**].

5.8   **Evaluation of HPV Linear Array Genotyping.**

The development of low-cost and reliable methods for identification of specific types of HPV virus carried by a patient is an issue of great interest for NCI researchers in the field of uterine cervix cancer. HPV genotyping methods might have clinical applications if they are approved by the FDA. One such method is the Roche Linear Array HPV genotyping test. In this test, patient specimen material is applied to a specially-manufactured "linear array strip". This strip is divided into a linear array of rectangular, non-overlapping cells, each of which reacts to the DNA of a specific type of HPV virus. The cell reactions consist of darkening in color, depending on the strength of the HPV signal detected, and the strips are typically interpreted by human observers, who classify them on a six-level scale: 0=negative (no perceptible darkening of the cell); 1=extremely weak (just-perceptible darkening); 2=very weak; 3=weak; 4=moderate; 5=strong (very dark). Each strip has 37 cells and potentially detects up to 37 genotypes for a single patient. From 12 to 20 strips are typically arranged side-by-side and photographed with a digital camera; then the digital images are evaluated by an expert. This evaluation procedure is very time-consuming, prone to error, and is believed to be highly susceptible to inter- and intra-observer variability. Hence, it is of great interest to determine whether automated methods may be used to interpret the strips with performance as good as or better than human observers.

An initial study was carried out by NCI [**19**], using the NLM-developed HPV Linear Array Tool. The study was based on linear array strips collected in the NCI-sponsored *Study to Understand Cervical Cancer Early Endpoints and Determinants* (SUCCEED) at the University of Oklahoma. A total of 1,018 strips (37,666 cells) were used in the study. The strips had been previously interpreted by human observers, and for each cell, a visual evaluation was made that assigned an HPV signal response level, using the 0-5 scale previously described. For each visual category, quantitative signal measurements made with the HPV Linear Array Tool for cells in that category were analyzed. Results showed that:

> The interquartile ranges of the measured intensities were statistically significantly different between all visual categories and between the positive and the negative category…Nonetheless, there was substantial overlap, especially for the negative, extremely weak, and very weak visual signals.

The NCI researchers concluded that, despite the overlap in signal values across visual categories, the visual and automated signals were highly correlated. Further, they used the automated measurements as a reference to explore the hypothesis, which had been suggested by earlier work, that the presence of multiple signals on a strip (i.e., for one patient) induced an "optical bias" that influenced an observer to classify a cell of ambiguous visual appearance as positive for HPV. Their results are given here:

We found that for automatically measured signal strengths between 20 and 119 units, there was a significant trend: equivocal signals were increasingly likely to be called positive by the naked eye as the number of other definite signals on the same strip increased…

In addition, the researchers detected several errors in the visual readings by use of the automated software:

In our detailed comparison of the visual and automated methods for the evaluation of LA strips, the optical software found nine visual readings that were clearly misclassified. These nine misclassified signals occurred on four LA strips. In one case, an erroneous genotype was assigned to a signal that corresponded to the location of an adjacent HPV probe on the strip. Two strips were affected when a signal in one strip was attributed to the neighboring strip. In the fourth case, the genotype pattern reported visually was totally different from the automated results, suggesting a coding error.

…our study found only nine clear, nonsubtle misclassified signals from four different cases [i.e., patients]. This total could be considered a small number, because 1,018 samples were processed; however, in all four cases the mistake involved high-risk HPV types, showing that the results could have clinical implications for the women.

The researchers concluded:

Standardization of HPV typing is worth the effort because it forms the basis for HPV research and might play a central role because of its role in defining the persistence of HPV, in clinical decision making for patient management, and even in treatment. Any gain in precision and reliability is urged for the better and more adequate clinical management of the millions of women who are infected with HPV.

6   Impact in colposcopy knowledge assessment for medical professionals

6.1   **Image-based testing for a national program of knowledge assessment in colposcopy.**

Working with NCI and the American Society for Colposcopy and Cervical Pathology (ASCCP), NLM engineers have developed the Teaching Tool application to provide Web-based knowledge assessment for medical professionals in the field of colposcopy. The Teaching Tool software currently supports two ASCCP exams, the Colposcopy Mentorship Program (CMP) exam, and the Resident's Online Exam (ROE). Each exam consists of three parts: (1) a text-only multiple choice section that addresses proficiency in general colposcopic knowledge; in management of patients with both high- and low-grade cervical neoplasias; and in management of adolescents; (2) an image-based "slide ID" section that tests the ability to visually interpret pathology characteristics of the cervix, vulva, and vagina; and (3) an image-based "cases" section, where each case consists of a triple of diagnosis, biopsy, and management questions for a single patient; for the biopsy question, the test-taker uses the mouse to position a crosshair on the image where he/she would take a biopsy.

The image data for these exams comes from the images digitized by NLM from the NCI Guanacaste and ALTS projects, with some supplemental images provided by the ASCCP. All question content was defined by the ASCCP, in consultation with NCI. The selection of the

particular images to use, and the marking of acceptable biopsy areas, was done by NCI and the ASCCP, using NLM's Boundary Marking Tool.

NLM has participated not only as a tool developer, but as a collaborator in content creation for the Teaching Tool's use by the ASCCP. This work has included making the Teaching Tool accessible for beta testing from a public Web site, image processing for cropping, scaling, and enhancing the images, and refining of the exam content in collaboration with the ASCCP. After the first beta test was conducted with 13 medical professionals, in October-November 2008, modified content included image processing for enhancing dark images, and the modification of some case management questions to bring them into conformance with updated clinical management protocols. The second beta test included 22 medical professionals and was conducted April-June 2009.

The Teaching Tool creates its exams at test time by drawing randomly from pre-defined question pools. For example, for the case questions, the four pools defined are cases that are (1) benign, (2) low-grade neoplasia, (3) high-grade neoplasia, and (4) cancer. The slide ID questions are drawn from pools that include benign and cancer images, as well as intermediate grades; vulva/vagina pathology, and visual features of dysplasia, such as atypical blood vessels.

Exams are automatically graded by the Teaching Tool, and administrative capabilities are provided to allow administrators with minimal technical expertise to add testers, assign exams, and view results, including cumulative results down to the individual question level. Using these capabilities, an analyst may, for example, create a report showing how testers performed on a selected subset of questions or images over a specified time interval.

As discussed above, two beta tests coordinated by the ASCCP have been done with the Teaching Tool. The latest was conducted April-June 2009 and had 22 participating medical professionals, predominantly gynecologists. The beta tests have resulted in changes to the exam content by removing unsatisfactory images, brightening dark images by image processing, adjusting ambiguous biopsy boundaries used to score correct biopsies, and modifying questions for clarity and conformity with prevailing clinical practice guidelines.

The refinements to the exam content that resulted from the second beta test are now being incorporated, and the ASCCP intends to move forward with the operational use of the Teaching Tool for its national testing program.

7 Next steps

While our principal work discussed in this report is the development and evaluation of practical tools for cancer research, and their timely dissemination for field use, we are cognizant of the problems posed by the acquisition of large image collections, the extraction of key data from the images, and the need for effective indexing, search and retrieval. This is the case for our cervigrams, histology images and other research collections, but also for clinical collections generated by Picture Archiving and Communication Systems (PACS) and Hospital Information Systems (HIS) that hospitals use to acquire, store and organize patient data. Indexing and

retrieval of images in these PACS and HIS systems, our image repositories, as well as broader collections in other domains, is conventionally done using text keywords in special fields (e.g., unique patient identifier, or fields in the image header).

Since these keywords do not capture the richness of features depicted in the image itself, our next steps involve research in Content-Based Image Retrieval (CBIR) to introduce automation in the acquisition of data from our collections, as well as in indexing the images by visual content. CBIR has received significant attention as a promising approach to ease the management of large image collections in several domains [**20, 21**], and more recently in applying it to medical image repositories [**22**]. Rather than limiting queries to textual keywords, CBIR would, by itself or in combination with text, allow users to query by example image or image feature (e.g., color, texture, or shape computed from a region of interest) to find similar images of the same modality, anatomical region, and disease along with the matching associated text records.

In this section we outline our work toward the next generation of some of the cancer research tools described in Section 4. As strategic initiatives in line with NLM and NIH Long Range goals listed in Section 2, these projects fall into three broad areas: (i) *image indexing and retrieval;* (ii) *geographically distributed collaborative systems*; and (iii) in *distributed computing to improve image indexing*.

7.1 **Image indexing and retrieval initiatives**

Our research efforts toward exploiting visual content for image indexing and retrieval have yielded tools for each major stage of the CBIR process, viz., segmentation, feature extraction, indexing, and retrieval. Some of the tools developed with a view to enhancing and aiding uterine cervix cancer research are:

- *Cervigram Segmentation Tool (CST):* A collection of algorithms with successful outcomes from our research in cervix region segmentation on cervigrams.
- *Multi-Observer Segmentation Evaluation System (MOSES):* A tool to evaluate the automatic image segmentations and expert-marked boundaries.
- *CervigramFinder:* A tool to extract visual features, such as shape, color, texture, location, and size, from segmented regions and provide a user interface for retrieving visually similar cervigrams.

Some of these tools have their roots in our prior research with digitized spine x-ray images from the second National Health and Nutrition Examination Surveys (NHANES II). This earlier work has been presented at previous BSC meetings [**23, 24**].

7.1.1 *Cervigram Segmentation Tool (CST)*

The segmentation and extraction of tissue regions in cervigrams is an important task that is routinely done manually. This often leads to high interpersonal variability in subsequent analysis of the images. A tool developed to automate steps in the process can assist in identifying important tissues and regions on cervigrams while achieving uniformity of the results.

CST [**38**] is a prototype Web-accessible system that integrates algorithms shown to be reliable for automated segmentation of cervigrams. It provides a framework for modular access through Java Web Start technology to the algorithms [**25, 26, 27**] we have typically developed as MATLAB prototypes. At its current stage of development, CST supports a multi-stage algorithm

that first identifies and eliminates small and bright regions of specular reflections caused by camera flash due to the presence of fluids. Subsequent algorithm stages localize three important tissue types (squamous epithelium, columnar epithelium, and acetowhite) and the os based on their appearance. These regions may serve as biomarkers for onset of disease, e.g., the space where CE and SE are clearly established (the transformation zone) and where the majority of cervical cancers start. Another important predictor of lesion severity is the vascular abnormality inside acetowhitened areas, viz., punctation, mosaicism, and atypical vessels. We have ongoing research in the automated analysis of all these important landmarks and tissues, though our algorithms are at different degrees of maturity. The modularity and Web-accessibility of the CST permit inclusion of promising but relatively immature algorithms in the tool. New or enhanced algorithms can be easily added to the tool as a server-side component.

### 7.1.2   MOSES: Multi-Observer Segmentation Evaluation System

The BMT, described in Section 4, allows multiple experts to mark regions of interest on cervigram images. However, it has been observed that there can be significant inconsistencies among the experts in marking the boundaries (inter-personal observation error). In addition, inconsistencies are also observed when same image is offered to the expert at different times (intra-personal observation error). Inter- and intra-personal inconsistencies in medical image annotation have frequently been observed, but rarely have they been quantitatively evaluated. MOSES enables oncologists evaluating observer-recognition of the visual expression of the disease to quantitatively assess the agreement among multiple experts. These disagreements, though often minor in spatial spread, can be significant in identifying biopsy sites, for example. Also, since these markups serve as training data for automated machine-learning-based image segmentation algorithms in use in the CST, a tool such as MOSES is needed to quantitatively evaluate and compare multiple segmentations (each by a different observer), and generate a ``true'' segmentation that achieves a higher degree of agreement. Further, the tool should enable image processing algorithm designers to evaluate the performance of their automatic (and semi-automatic) image segmentation algorithms against each other and / or an expert (or combined multiple-expert) truth [**28, 29**].

As a Web-based software application shown in **Figure 19**, MOSES implements such a flexible segmentation evaluation framework for digitized uterine cervix images. It is intended to assist researchers in two communities, viz., image-processing and cancer research, in evaluating image region boundaries marked by multiple observers. The tool uses boundary markup information exported from the BMT and can be used for all image types that can be marked using it. It overcomes a shortcoming in a popular algorithm described in the literature, STAPLE (Simultaneous Truth And Performance Level Estimation) [**30**], which is an Expectation-Maximization (EM) algorithm that probabilistically estimates the true segmentation by optimal combination of observed segmentations and a prior model of the truth. However, accurate modeling of the initial truth prior is nontrivial and in STAPLE the truth prior tends to dominate even when meaningful observer-performance priors are available. In contrast, MOSES uses a Bayesian decision formulation that combines multiple-observer segmentations based on the maximum a posteriori (MAP) principle that respects the observer prior regardless of the availability of the truth prior. It permits the two types of prior knowledge to be integrated in a complementary manner in four cases with differing application purposes: (1) with known truth prior; (2) with observer prior; (3) with neither truth prior nor observer prior; and (4) with both

truth prior and observer prior. Sensitivity (*p*) and specificity (*q*) are used to measure the performance level of the binary segmentation. Here, sensitivity is the fraction of pixels properly included in the segmented region out of all pixels in the segmentation result, and, specificity is the fraction of pixels properly excluded from the segmented region out of all pixels outside of the ground truth. A probabilistic combination of multiple observer segmentations is usually presented as a multiple-observer ground truth map, as shown in **Figure 20**.
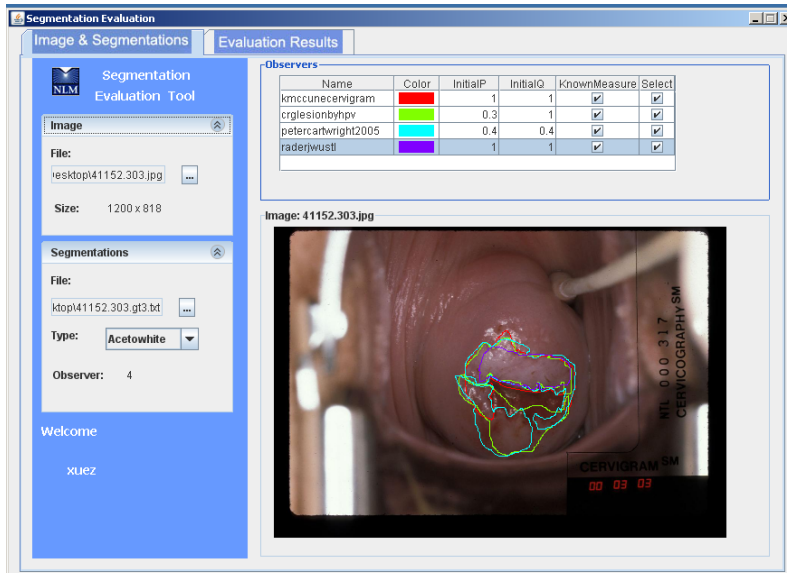
Figure 19 MOSES screenshot showing color-coded boundary markup by several experts.

| (a) | (b) |
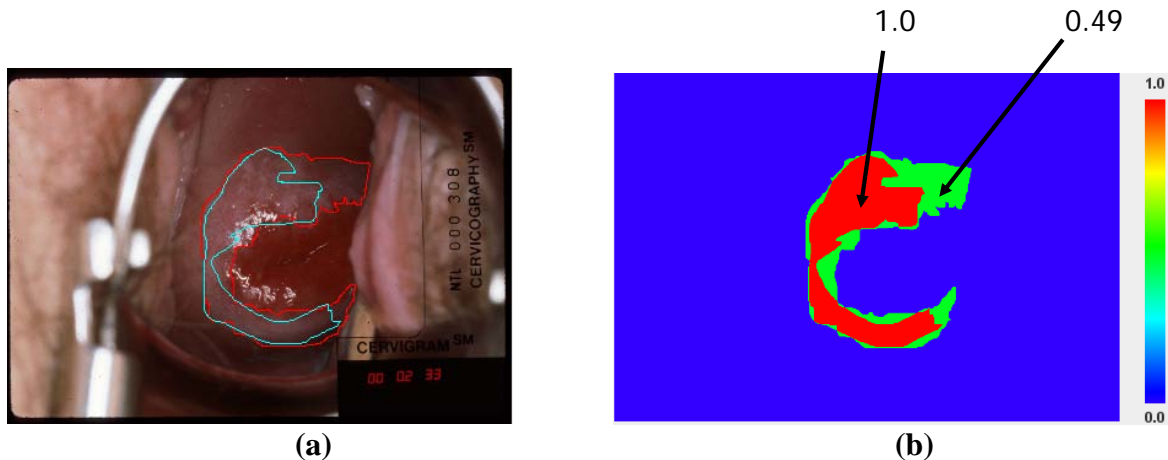
Figure 20 (a) Two observers' segmentations of acetowhite regions. (b) Multi-expert ground truth map.

7.1.3   CervigramFinder: Content-Based Image Retrieval Tool

The MDT provides text search capability to access the study results from Guanacaste and ALTS data that include clinical text data. In addition to the fielded text response the system can also retrieve and show digitized cervigrams and other images associated with the clinical record. However, to conduct studies similar to [**11**] which showed higher presence of visual abnormalities on the cervix when infected with HPV16 than other types, it is necessary to be able

to search for cervigrams by their visual appearance regardless of their diagnostic outcome. This feature is lacking in the MDT and is a targeted next step in its development.

Toward meeting this goal, we are designing a prototype CBIR system called CervigramFinder, shown in **Figure 21**. In its current form, it is a Web-based system for retrieving cervicographic images from a database using visual queries. It incorporates fundamental CBIR functions, such as feature extraction, normalization, dimension reduction, combination, and various similarity measures [**31, 32**]. Methods selected for the system resulted from an extensive performance evaluation of key techniques for cervigram retrieval that include use of color, texture, size, and location features [**33, 34**]. The features are normalized using Gaussian normalization and then combined using a weighted linear combination method. For practical Web-based use a Minkowski-form distance measure is used as the similarity metric.
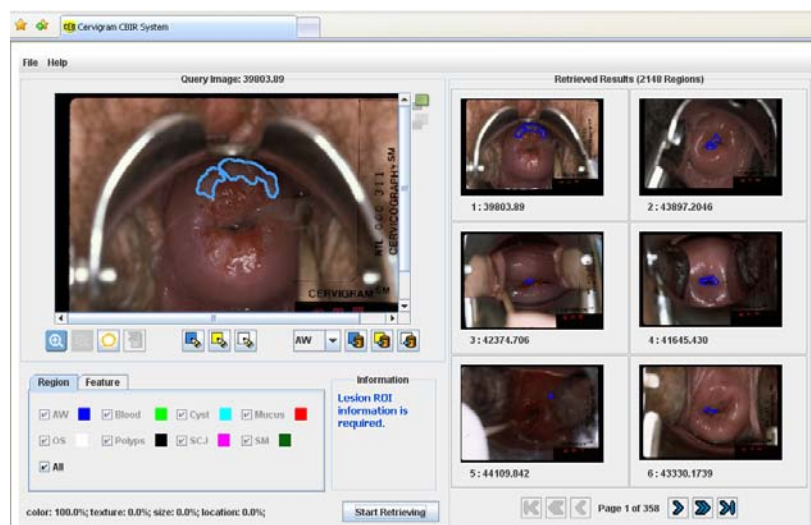
Figure 21 CervigramFinder screenshot showing retrieval results.

7.2 Collaborative systems initiatives

It is increasingly becoming evident that present day high impact clinical research is a community activity that requires collaboration and data sharing. Computing resources and tools must be developed to be interoperable with collaborative grid infrastructures such as caBIG[3]®. Computing initiatives such as these permit applications that are interoperable to share data and allow them to be used at different sites. An example data warehouse is NCI's National Biomedical Imaging Archive (NBIA) where efforts have concentrated on data collection and transmission, but have left development of applications to the research community. Even here the effort is limited to compliance for data sharing. Next steps in this direction would be *compute interoperability*. Even though most systems are opening up to data sharing, they tend to keep advanced implementations closed to sharing. Several community license models have made code sharing easier. However, actually deploying these source codes into individual projects is not trivial. We propose to overcome these shortcomings by defining a data and resource exchange framework using open standards and software to enable such specialized systems to act as geographically distributed toolkits. The approach enables communication between two or more

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[3] https://cabig.nci.nih.gov/

systems that are geographically separated but complementary systems. These systems may have different architectures, and may be developed on different platforms, and specialized for different image modalities and characteristics. The resulting combined system provides the user with a rich functionality and is independent of location and underlying user operating systems.
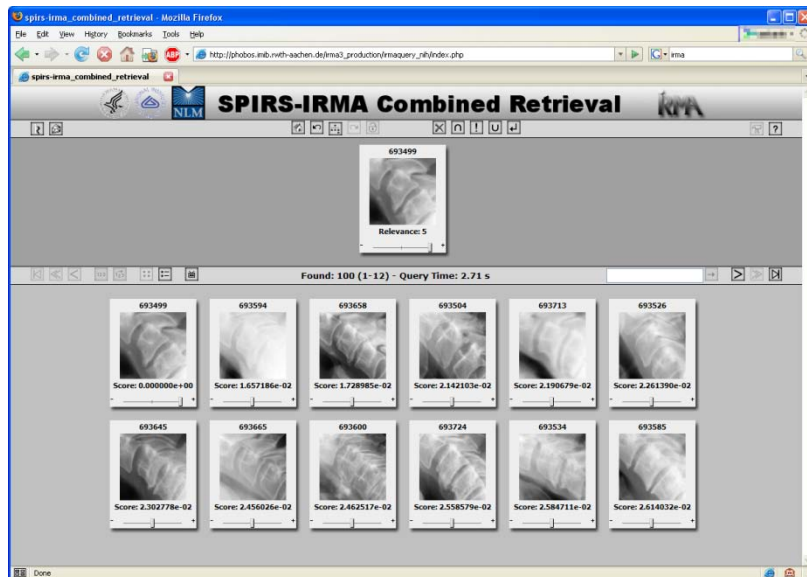

Figure 22. SPIRS-IRMA Geographically Distributed CBIR System

As proof-of-concept, we have coupled two leading, complementary, geographically separated image informatics CBIR systems: The Image Retrieval in Medical Applications[4] (IRMA) project at the Aachen University of Technology (RWTH) and our SPIRS system at NLM [**35, 36**]. IRMA and SPIRS retrieve images based on different approaches: IRMA implements image retrieval by computing overall (or global) image characteristics such as color, intensity, and texture. Such an approach permits queries on a varied image collection and helps identify similar images, e.g., *all chest X-rays in the A-P view*. However, it lacks the ability to find particular pathology that may be localized in specific regions within the image. In contrast, SPIRS can retrieve images that exhibit pathology that may be localized to a particular region, but assumes that the query is to a homogenous image collection containing images of only one type, e.g., *vertebral pathology expressed in spine x-ray images in the sagittal plane*. SPIRS lacks the ability to select pertinent images from a large varied image collection typical in a hospital PACS system, for example. Combining the strengths of these two complementary technologies of whole image and local feature-based retrieval is unique and valuable for research into the retrieval of images in large repositories that are similar in type as well as pathology. In the joint system, IRMA serves as the front-end for the end user, while SPIRS provides specific shape similarity algorithms and supplies formatted responses to structured queries. Future development phases will allow users to upload their own images, as in the current IRMA system, as well as segmented or sketched boundary outlines of interest. Next steps include multi-resolution shape queries and support for query logging and relevance feedback. A screenshot of the combined SPIRS-IRMA system is shown in **Figure 22**.

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[4] http://www.irma-project.org

NLM's efforts in developing this concept of geographically distributed image computation systems with applications to clinical research was recognized by the Internet2 community for its 2008 Internet2 Driving Exemplary Applications (IDEA) Award. Internet2 is a consortium of universities, companies, government, and research labs. The IDEA awards recognize innovators who have created and deployed advanced network applications that have enabled transformational progress in research, teaching, and learning.

7.3 **Distributed high performance computing initiatives**

To be effective and useful, real-world applications of biomedical image analysis, indexing, and retrieval will need to address the computational challenges posed by the high processing time required for image analysis, and the large (and increasing) number of images acquired in biomedical research and clinical medicine. Offloading compute-intensive processing would potentially provide significant advantages in reducing the time taken for key tasks: indexing the database initially, re-indexing when indexing features are improved or modified, searching large multidimensional index structures. Computing features from medical images is time-consuming on conventional workstations, and can consume days of compute time even for modestly sized datasets on the order of 50,000 images. Reducing this time by even one order of magnitude would be a significant step, for the freeing up of computing resources alone.

To identify effective low-cost high-performance computing solutions we have explored the use of stream processing approaches using graphics processing units (GPU) and game consoles, and distributed lazy cycle computing. For example, overall speedups of 400% have been achieved by our ongoing research to segment biomedical images using Active Contour segmentation algorithms optimized for using GPUs. We have also explored using low-cost, low-power (green) alternatives to GPUs through use of a cluster of game consoles, such as the Sony PlayStation 3® (PS3). In this effort we have observed 7X speedup on color space conversion and Gabor filter computation, and more impressive numbers for image resizing, when compared with optimized routines running on a current generation quad-core multiprocessor desktop **[37]**. Finally, as an alternative to high performance architectures, we are also exploring distributed computing approaches that utilize lazy-cycles of idling computers on a network. For example, CEB has 50 or more workstations that are actively used during the day, but are often not used at night. There is an opportunity to exploit these resources for image processing if a networking computing system can be implemented which would allow the allocation of the available machines to parts of an overall, large image computational problem, in a controlled and efficient manner. Such systems are typified by the Berkley Open Infrastructure for Network Computing (BOINC), which supports the use of ordinary workstation computers for the solution of very large data processing tasks (some well-known ones being the Folding@Home and SETI@home programs which report a sustained 7 PFLOPS and 528 TFLOPS of computation, respectively[5]).

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[5] http://en.wikipedia.org/wiki/List_of_distributed_computing_projects

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